

# Australian Diabetes Society

A.B.N. 13 053 787 965 A.C.N. 053 787 965

The Peak Medical and Scientific Health Professional Body on Diabetes in Australia

## **ADS Position Statement on rosiglitazone (AVANDIA®) and cardiovascular outcomes**

This is a revision of our previous position statement concerning Rosiglitazone and cardiovascular outcomes. ADS recognise that this is an important issue of concern to practicing clinicians that requires further investigation and elucidation. The purpose of this statement is to provide guidance to Australian doctors.

ADS Council has considered a number of articles including the following, their accompanying editorials and others in formulating this position statement, some of the articles are listed at the end.

While it is clear and undisputed that thiazolidinediones can cause heart failure, there has been controversy about the association between rosiglitazone and cardiovascular outcomes. Two meta-analyses have examined the association between rosiglitazone and cardiovascular death. The first included 14376 patients from many small studies and the DREAM and ADOPT studies. There was a 1.43 OR for myocardial infarction ( $p=0.03$ ) and an OR of 1.64 for cardiovascular death ( $p=0.06$ ) (1). The second, which included 20191 patients from 7 studies found no alteration in risk of cardiovascular death with either rosiglitazone or pioglitazone with RR 0.93 (2).

Since these two papers, results of the ACCORD (3), ADVANCE (4) and RECORD (5) studies have been published. In the ACCORD trial, a significantly increased risk of death from any cause and death from cardiovascular death in the intensively treated group was observed. The study was designed to achieve near-normal glycaemia in a population of people with relatively long-standing diabetes. In the intensively treated group, 92% of patients received a thiazolidinedione, predominantly rosiglitazone. No increase in mortality was seen with intensive therapy in the ADVANCE trial which had 58% use of thiazolidinediones. The RECORD study was an open label study of 4447 patients who received either addition of rosiglitazone as dual therapy with metformin or sulfonylurea *or* metformin+sulfonylurea. Hazard ratio was 1.14 ( $p=ns$ ) for myocardial infarction, and 0.84 for cardiovascular death ( $p=ns$ ).

There have already been many commentaries published on this issue, as editorials or statements. Regulatory authorities including the US Food and Drug Administration, the European Medicines Agency and the Australian Therapeutic Goods Administration have stated their position. Professional bodies including the (American) Endocrine Society, American Association of Clinical Endocrinologists and jointly the American Diabetes Association, American Heart Association and American College of Cardiology have also released statements. Diabetes Australia has developed a position statement mainly for the information of people with diabetes. ADS agree with the advice given

### **Executive Committee**

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by Diabetes Australia that patients should not stop Avandia® without consultation with their doctor.

A review of the statements released by the above bodies reveals clear agreement that:

1. The possible association between rosiglitazone and cardiovascular events is of extreme importance
2. The currently available evidence taken in its entirety does not allow a definitive statement on the safety or risk of rosiglitazone in this context.
3. The Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) study did not confirm a significant cardiovascular risk with rosiglitazone.
4. To date, apart from advisories, the above regulatory authorities have not withdrawn or limited the indications or availability of rosiglitazone.

## **RECOMMENDATIONS**

ADS strongly recommend that doctors fully discuss the study results with their patients currently on or about to commence rosiglitazone. The discussion should also address the proven value of glycaemic control in reducing the risk of microvascular complications of diabetes. ADS further recommend that the options for management be discussed with patients. These options include:

1. Continuation of rosiglitazone while awaiting further evidence in patients without heart failure. ADS council considers this a reasonable option at this time.

Or

2. Discontinuation of rosiglitazone AND maintenance of glycaemic control by:
  - a. The use of alternative oral hypoglycaemic agents from either the same or another class
  - b. The commencement or adjustment of insulin

While ADS do not consider the current evidence allows a definitive recommendation on the use of rosiglitazone except in the setting of known heart failure, it is prudent practice to advise alternative management if a patient has ongoing concern after discussion. ADS emphasises that comprehensive management of diabetes should always include cardiovascular risk assessment and treatment. Our Australian PBS guidelines do not recommend the use of rosiglitazone with insulin, or for initiation for triple oral therapy.

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For the information of Australian doctors – The United States Department of Veteran Affairs has recently announced that it withdrew rosiglitazone (Avandia ®) from its formulary as of 5<sup>th</sup> October 2007 after concluding that the treatment “may not afford the same margin of safety as alternative therapies in some patients.” This decision has been taken subsequent to the decision of the FDA in July that Avandia remain available in the United States despite the FDA’s concern that there was an increased risk of ischaemic cardiovascular events with Avandia.

Potential conflict of interest statements relevant to rosiglitazone (Avandia):

ADS receive support for the ADS Annual Scientific Meeting from GSK as a principal sponsor and has had standard commercial arrangements with GSK to display at the ADS Scientific Meeting.

Stephen Twigg, Ashim Sinha, Jenny Gunton, Michael d’Emden, Wah Cheung have received honoraria, travel support or payment for participation in GSK advisory committees.

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1. Nissen SE, Wolski K. Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes. *N Engl J Med.* 2007 Jun 14;356(24):2457-71
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4. The ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;358:2560-72.
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