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Assessment report for AVANDAMET

International Non-proprietary Name: rosiglitazone plus metformin

Procedure No. EMA/H/C/000522/A20/0063

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Executive summary

Rosiglitazone was first approved in 1999 in the United States and in 2000 in the European Union as Avandia. Rosiglitazone is also authorised in the EU since 2003 as Avandamet (fixed dose combination with metformin) and since 2006 as Avaglim (fixed dose combination with glimepiride). Rosiglitazone (RSG) is a member of the thiazolidinedione (TZD) class of antidiabetic agents.

On June 28th, after the 2010 renewal opinion, new data emerged, suggesting that rosiglitazone may be linked to an increased risk of heart problems. An update of the meta-analysis by Nissen et al initially published in 2007 raised concerns regarding the cardiovascular safety of rosiglitazone. A retrospective observational study performed by Graham et al was also published concerning the cardiovascular safety of rosiglitazone.

On the basis of this new information, the European Commission (EC) initiated a procedure under Article 20 of Regulation (EC) No 726/2004, requesting the CHMP to assess the impact of this new information on the benefit-risk balance for the centrally authorised rosiglitazone-containing medicinal product and to give its opinion on measures necessary to ensure the safe and effective use of rosiglitazone-containing medicinal products and on whether the marketing authorisation for these products should be maintained, varied, suspended or revoked.

2. Background information

Rosiglitazone (RSG) is a member of the thiazolidinedione (TZD) class of antidiabetic agents, together with pioglitazone (PIO). TZDs improve glycaemic control by improving insulin sensitivity at key sites of insulin resistance by binding to nuclear peroxisome proliferator-activated receptor gamma in adipocytes to promote adipogenesis and fatty acid uptake. By reducing circulating fatty acid concentrations and lipid availability in liver and muscle, the drugs improve the patients' sensitivity to insulin. This mechanism is unique to the TZD class.

Rosiglitazone was first approved in 1999 in the United States and in 2000 in the European Union as Avandia. Rosiglitazone is also authorised in the EU since 2003 as Avandamet (fixed dose combination with metformin) and since 2006 as Avaglim (fixed dose combination with glimepiride).

Avandia is currently approved in the EU for use as monotherapy in patients with type 2 diabetes mellitus (T2DM) patients, particularly overweight patients, who cannot take metformin, as dual therapy in combination with metformin (MET) or sulphonylurea (SU), or triple therapy in combination with metformin and sulphonylurea.

Avandamet is currently approved in the EU in the treatment of type 2 diabetes mellitus (T2DM) patients, particularly overweight patients who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin (MET) alone or in triple oral therapy with sulphonylurea (SU) in patients with insufficient glycaemic control despite dual oral therapy with their maximally tolerated dose of metformin and a sulphonylurea.

Avaglim is currently approved in the EU in the treatment of type 2 diabetes mellitus (T2DM) patients who are unable to achieve sufficient glycaemic control on optimal dosage of sulphonylurea (SU) monotherapy, and for whom metformin (MET) is inappropriate because of contraindication or intolerance.

Regulatory background

Initial marketing authorisation

At the time of the initial marketing authorisation (MA), the CHMP was satisfied with the short-term safety of rosiglitazone, but the available data on long-term safety was at the time considered to be limited. However, additional studies looking at more sensitive functional parameters to detect early onset of cardiac injury as well as studies evaluating the potential of rosiglitazone to affect cardiovascular morbidity and mortality in diabetes patients during long-term therapy were required. The CHMP therefore only granted a second line indication as add-on to MET or SU. A contraindication for use of rosiglitazone in patients with congestive heart failure or history of congestive heart failure (New York Heart Association (NYHA) functional classification stages I to IV) as well as a warning

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regarding the possible development of fluid retention and congestive heart failure were included in the Summary of Product Characteristics (SPC). Rosiglitazone was also contraindicated in combination with insulin. As requested by the CHMP, the Marketing Authorisation Holder (MAH) committed to perform a double blind study of the effect of rosiglitazone on cardiovascular structure and function in type 2 diabetic patients with chronic heart failure NYHA stages I-II (which became study 211) and a long-term cardiovascular morbidity/mortality study in patients on rosiglitazone in combination with SU or metformin (which became the RECORD study).

2007/2008 benefit-risk assessment

In 2006, the World Health Organisation (WHO) published an analysis of spontaneous adverse reaction reports from the WHO database which revealed disproportionate reporting for events of heart failure and myocardial ischemia for both rosiglitazone and pioglitazone. Following this analysis, the marketing authorisation holder performed an integrated clinical trial (ICT) analysis of safety data from the clinical trials program for rosiglitazone. This analysis, referred to as ICT 42, evaluated events of congestive heart failure and myocardial ischaemia encompassing 14,237 subjects included in 42 double-blind, randomised controlled trials of varied design and populations of patients with type 2 diabetes (including those with pre-existing congestive heart failure and those on background insulin therapy). The incidence of myocardial ischemia events was 1.99% for rosiglitazone-containing regimens and 1.51% for comparator regimens (hazard ratio (HR) 1.31, 95% confidence interval (CI) 1.01–1.70). This information was added to the product information through variation EMEA/H/C/268/II/47 (opinion September 2006).

On 21st May 2007, a meta-analysis of 42 trials by Nissen et al. (see reference 1.) indicated an increased cardiovascular risk associated with rosiglitazone. The analysis resulted in an increase of about 40% in the risk of myocardial infarction among patients receiving rosiglitazone as compared with those receiving either an alternative oral diabetes therapy (metformin or sulphonylurea) or placebo.

In 2007/2008, due to these safety signals as well as the finding of an increased risk of bone fractures, the CHMP performed an in depth re-evaluation of the benefits and risks associated with the use of rosiglitazone based upon available data up to July 2008. This assessment included available data based on randomised controlled trials (e.g. the ADOPT and DREAM studies), meta-analyses as well as observational.

The main conclusions of the benefit-risk assessment was that the data on the risk for ischaemic heart disease (IHD) was inconsistent and the CHMP considered that rosiglitazone had a place in the treatment of patients with type 2 diabetes after careful individual benefit risk assessment and provided that all the precautions and warnings included in the product information are adhered to. The product information was updated to include a contra-indication for patients with acute coronary syndrome (ACS), a warning stating that rosiglitazone may be associated with an increased risk of myocardial ischaemic events and a precaution that rosiglitazone should not be used in patients with myocardial ischaemic symptoms. The Scientific Advisory Group (SAG) Diabetes/Endocrinology was also consulted in September 2008 and concluded that overall rosiglitazone retained a small, though diminishing place in therapy. No further restrictions to its use in addition to those already included in the PI were considered necessary.

Data submitted by the MAH after the benefit-risk review of 2007/2008, in the scope of follow-up measures (FUMs) and type II variations

- In April 2009, the study report from the APPROACH (Assessment on the Prevention of Progression by rosiglitazone on Atherosclerosis in Type 2 Diabetes Patients with Cardiovascular History) study was submitted and assessed in the FUM 037. The study was a phase III, 18 month, multicentre, randomised, double-blind, active-controlled clinical trial to compare rosiglitazone versus glipizide on the progression of atherosclerosis in subjects with T2DM and cardiovascular (CV) disease. The primary efficacy endpoint (change in percent atheroma volume) showed an increase in the glimepiride group (adjusted mean 0.43; SE 0.331) and a decrease in the rosiglitazone group (adjusted mean -0.21; SE 0.331) although this difference was not statistically significant (mean -0.64; CI -1.46-0.17).

- In September 2009, the MAH submitted the final study report from the long-term cardiovascular outcome study RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes), in which rosiglitazone was added to baseline treatment with MET or SU and also compared to these agents. Patients had a mean duration of diabetes of 6-8 years and 15-20% of the patients had IHD at baseline. The hazard ratio (HR) for the primary endpoint

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(time to first occurrence of CV death or CV hospitalization) was 0.99 (CI 0.85-1.16) and the HR for acute myocardial infarction (MI) (secondary endpoint) was 1.14 (CI 0.80-1.63). This study was assessed in the variation EMEA/H/C/268/II/71.

- In April 2009, the MAH submitted the ICT 52 data set analysis now including 52 rosiglitazone trials, as an update of ICT 42. This data was assessed in the FUM 041 and amendments to the SPC were introduced under the variation EMEA/H/C/268/II/71. The results were in general similar to the previous analysis including 42 trials, with HR for MI 1.45 (CI; 0.85-2.45) and 1.41 (CI 0.89-2.22), HR for major adverse cardiac events (MACE = MI, stroke, CV mortality) 1.06 (CI 0.71-1.59) and 1.12 (CI 0.79-1.59), for the 42 and 52-trials analyses, respectively.

- The MAH has undertaken to perform a large, multicentre controlled clinical trial, the TIDE (Thiazolidinedione Intervention With Vitamin D Evaluation) trial, which commenced in May 2009. It is expected to enrol 16 000 patients and completion is targeted for 2015-16. A secondary outcome of this trial is to compare rosiglitazone and pioglitazone with regard to CV death, MI, or stroke. The study protocol was submitted to and assessed by the CHMP.

2010 second renewal procedure

In the context of a renewal procedure for Avandia, concluded in March 2010, the CHMP was of the opinion that even though the benefit-risk balance of rosiglitazone was still considered as positive, the safety concerns associated with the use of rosiglitazone required further follow-up. In addition results from several studies were awaited to provide further answers on the risk of bone fractures and cardiovascular safety. The CHMP therefore recommended an additional renewal period of 5 years, rather than an unlimited renewal, together with the submission of yearly periodic safety update reports (PSURs). Additional data was also expected from the TIDE study.

New data emerging after the 2010 renewal opinion, triggering the Article 20 procedure

- An update of the meta-analysis by Nissen et al initially published in 2007 (see reference 2.) was published on June 28th 2010, raising concerns regarding the cardiovascular safety of rosiglitazone.

- A retrospective observational study performed by Graham et al (see reference 3.) was also published on June 28th 2010, concerning the cardiovascular safety of rosiglitazone.

On the basis of this new information, the European Commission (EC) initiated a procedure under Article 20 of Regulation (EC) No 726/2004, requesting the CHMP to assess the impact of this new information on the benefit-risk balance for the centrally authorised rosiglitazone-containing medicinal product and to give its opinion on measures necessary to ensure the safe and effective use of rosiglitazone-containing medicinal products and on whether the marketing authorisation for these products should be maintained, varied, suspended or revoked. The Article 20 procedure was started on 9 July 2010 and following initial discussions by the CHMP, input from expert groups, and an oral explanation held on 20 July, a List of Questions was adopted, to be addressed by the MAH. The MAH provided written responses which were assessed by the CHMP.

New data identified after the initiation of the Article 20 procedure

- An FDA briefing document was made public ahead of the Food and Drug Administration (FDA) Advisory Committee Meeting in the USA which took place on July 13-14, 2010. The aim of this meeting was to discuss the newly available data since the July 2007 FDA advisory committee meeting concerning the safety of rosiglitazone. These new data include:
    - an FDA meta-analysis of rosiglitazone and pioglitazone studies
    - an FDA review of Observational data
    - several assessments of the design and results of the RECORD study

- On June 28th 2010, the investigators from the BARI 2D (Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes) study presented their results during the American Diabetes Association (ADA) 2010 Scientific Sessions.

- An article on an observational study by Bilik et al. (see reference 4.) was published on May 27th 2010.

- An article on a retrospective study by Wertz et al. (see reference 5.) was published on August 24th 2010.

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3. Scientific discussion

3.1. Clinical aspects

3.1.1. Cardiovascular safety

Observational studies

Graham et al. Risk of Acute Myocardial Infarction, Stroke, Heart Failure, and Death in Elderly Medicare Patients Treated With Rosiglitazone or Pioglitazone, JAMA. published online June 28, 2010

Graham et al. conducted a study to assess whether the risk of acute myocardial infarction (AMI), stroke, heart failure (HF), and death in U.S. elderly (age 65 and above) Medicare patients is increased by rosiglitazone compared with pioglitazone. Medicare is the largest health insurance program in the United States. Eligibility for Medicare Part A, which covers hospitalization expenses, begins automatically at age 65 years, whereas coverage for outpatient medical care (Part B) and prescription drugs (Part D) must be purchased. The study was an observational, retrospective, inception cohort of 227 571 Medicare beneficiaries aged 65 years or older (mean age, 74.4 years) who initiated treatment with rosiglitazone or pioglitazone through a Medicare Part D prescription drug plan from July 2006-June 2009 and who underwent follow-up for up to 3 years after thiazolidinedione initiation. The individual end points were acute myocardial infarction (AMI), stroke, heart failure, and all-cause mortality (death), and the composite end point were AMI, stroke, heart failure, or death. The endpoints were assessed using incidence rates by thiazolidinedione, attributable risk, number needed to harm, Kaplan-Meier plots of time to event, and Cox proportional hazard ratios for time to event, adjusted for potential confounding factors, with pioglitazone as reference. To evaluate the nature and importance of the non-proportionality, a series of unplanned, post hoc analyses were performed. Furthermore, several pre-planned sensitivity analyses were performed (e.g. in subpopulations based on concomitant medications). The main results are summarised below in Table 1.

Incidence Rates, Attributable Risks (Rate Differences), and Numbers Needed to Harm for AMI, Stroke, Heart Failure, All-Cause Mortality, and a Composite Individual End Point in Elderly Medicare Patients Treated With Rosiglitazone vs Pioglitazone

End Point	Events, No.		Incidence Rate per 100 Person-Years		Attributable Risk (95% CI) per 100 Person-Years	No. Needed to Harm (95% CI), Person-Years	HR (95% CI)	
	Rosiglitazone	Pioglitazone	Rosiglitazone	Pioglitazone			Unadjusted	Adjusted[a]
AMI	523	1223	1.83	1.68	0.15 (–0.03 to 0.33)	NA[b]	1.07 (0.97-1.19)	1.06 (0.96-1.18)
Stroke	363	669	1.27	0.95	0.32 (0.17-0.47)	313 (213-588)	1.31 (1.15-1.49)	1.27 (1.12-1.45)
Heart failure	1125	2132	3.94	3.00	0.94 (0.68-1.20)	106 (83-147)	1.27 (1.18-1.37)	1.25 (1.16-1.34)
All-cause mortality	814	1748	2.85	2.40	0.45 (0.22-0.67)	222 (149-455)	1.17 (1.07-1.27)	1.14 (1.05-1.24)[c]
AMI, stroke, heart failure, or all-cause mortality	2593	5386	9.10	7.42	1.68 (1.27-2.08)	60 (48-79)	1.20 (1.14-1.26)	1.18 (1.12-1.23)[c]

Abbreviations: AMI, acute myocardial infarction; CI, confidence interval; HR, hazard ratio; NA, not applicable.
[a] Cox proportional hazards model stratified by history of cardiovascular end point and cancer and adjusted for variables in Tables 1-3.
[b] Attributable risk was not statistically significant.
[c] Test of proportional hazard assumption not met.

Table 1 - Source: Graham et al. JAMA. published online Jun 28, 2010

The CHMP considered the Graham et al study to be a well performed observational study in elderly patients. Limitations were noted, such as short follow-up, possible channelling from rosiglitazone to pioglitazone, lack of information on smoking or diabetes duration and lack of information on dosing and the dose-response relationship between rosiglitazone and pioglitazone and fluid retention and the potential risk for heart failure while a number of strengths were also noted, including a large sample size, access to registry data not affected by differential misclassification and detailed and well performed analyses. The CHMP noted that the results showed an increased risk of congestive heart failure (CHF) and all-cause mortality for rosiglitazone compared to pioglitazone, with increased adjusted HRs for rosiglitazone for stroke, heart failure, all-cause mortality, and the composite of AMI, stroke, heart failure, or all-cause mortality compared with pioglitazone, while there was no significant difference in adjusted HR for MI between the groups.

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The results corroborate previous findings of an association of rosiglitazone treatment in elderly patients and a small increase in the relative risk for cardiovascular diseases. However, the CHMP considered that the results of the study add weight to the concern that rosiglitazone treatment may carry an increased cardiovascular risk, compared to pioglitazone. Even if this potential risk is small in relative terms it may translate into an absolute risk that may be of importance in high risk groups. The CHMP considered the evidence from the Graham et al study to be robust and contributing to the overall benefit-risk assessment of rosiglitazone.

Reviews of observational data

The FDA systematically reviewed twenty one observational studies that examined comparisons of rosiglitazone and pioglitazone for outcomes including acute myocardial infarction, congestive heart failure and all-cause mortality. The results of the 21 observational studies reviewed varied; in general, most studies report MI data, with less information on other CV endpoints. In the FDA's analysis, comparisons of rosiglitazone and pioglitazone consistently favoured pioglitazone for acute myocardial infarction, congestive heart failure and all-cause mortality. The main results are summarised below in Table 2.

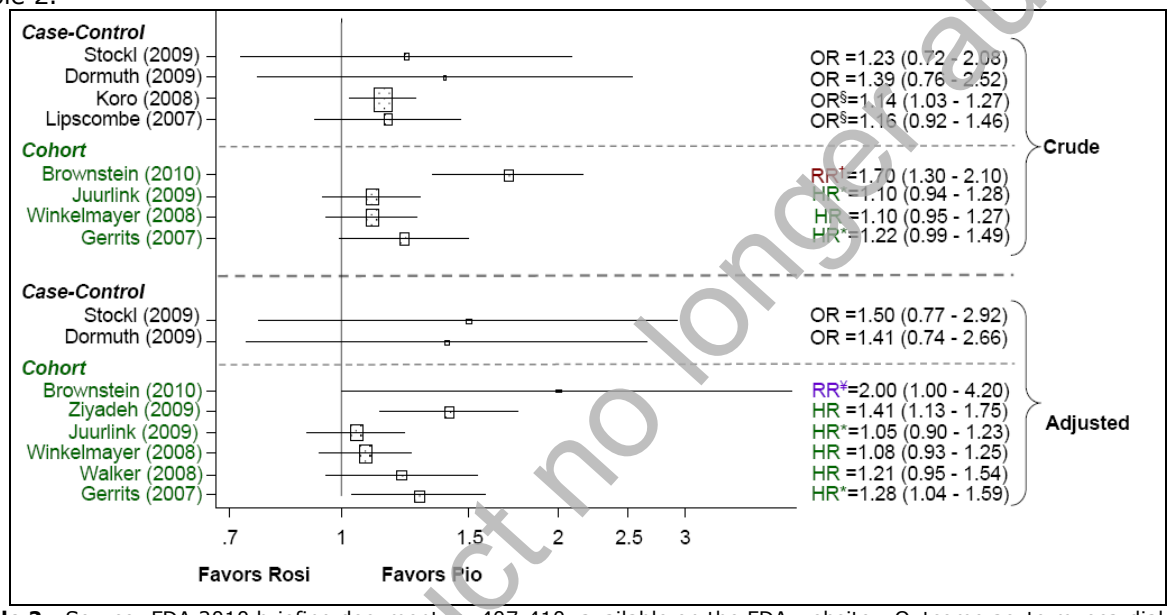

Table 2 - Source: FDA 2010 briefing document, p. 407-410, available on the FDA website - Outcome acute myocardial infarction (AMI): rosiglitazone versus pioglitazone

Two studies included in the FDA review were specifically limited to patient populations older than 65 or 66 years of age, derived from North American databases. Below are forest plots for the Winkelmayer et al (see reference 6.), 2008 and Juurlink et al (see reference 7.), 2009 studies, for congestive heart failure, all-cause mortality and stroke as shown in Figures 1, 2 and 3 below.

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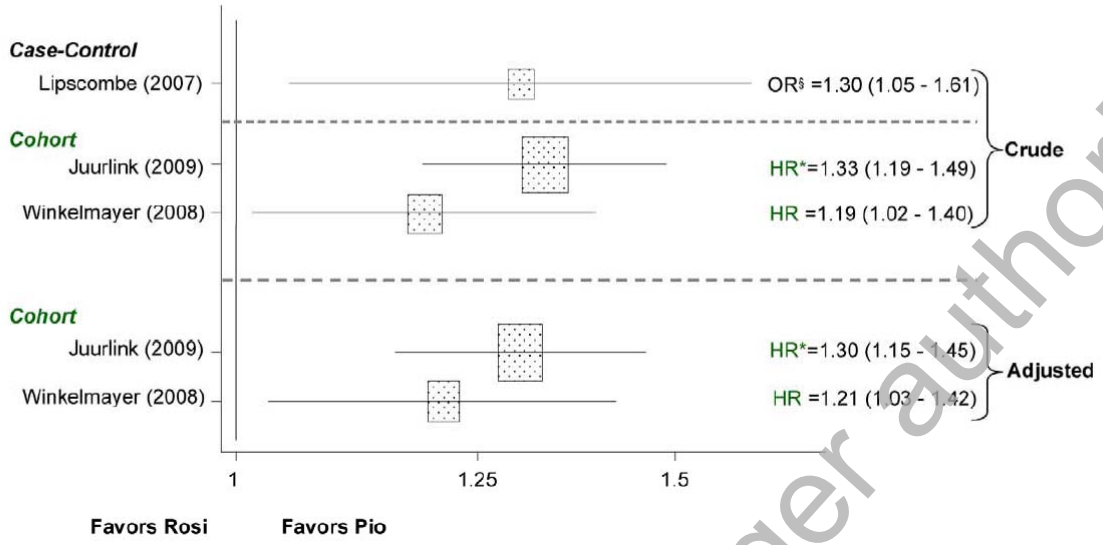
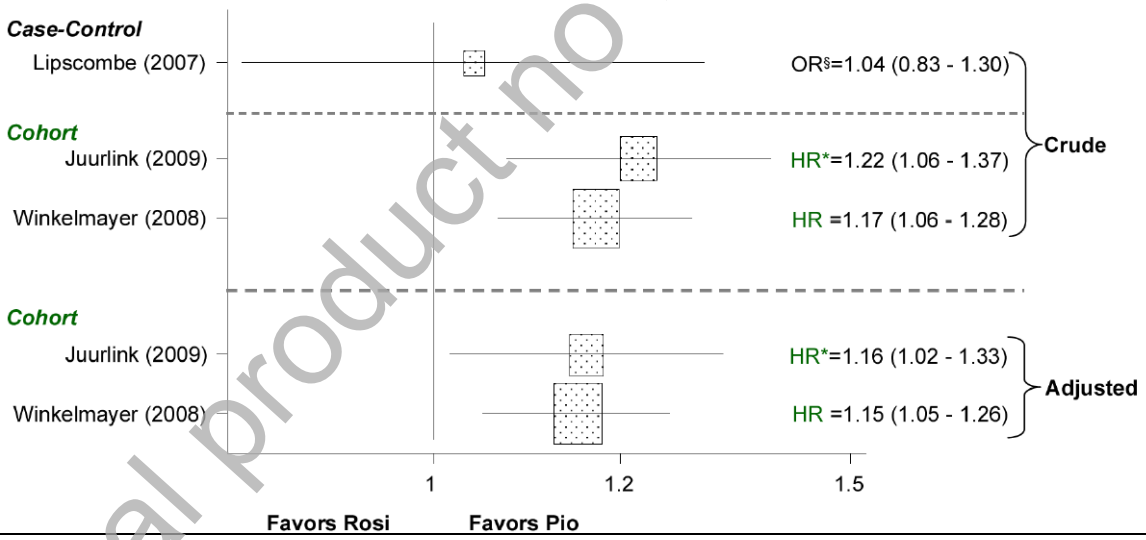
9.3.1.2 Outcome: congestive heart failure – rosiglitazone vs. pioglitazone



9.3.1.3 Outcome: all-cause mortality – rosiglitazone vs. pioglitazone



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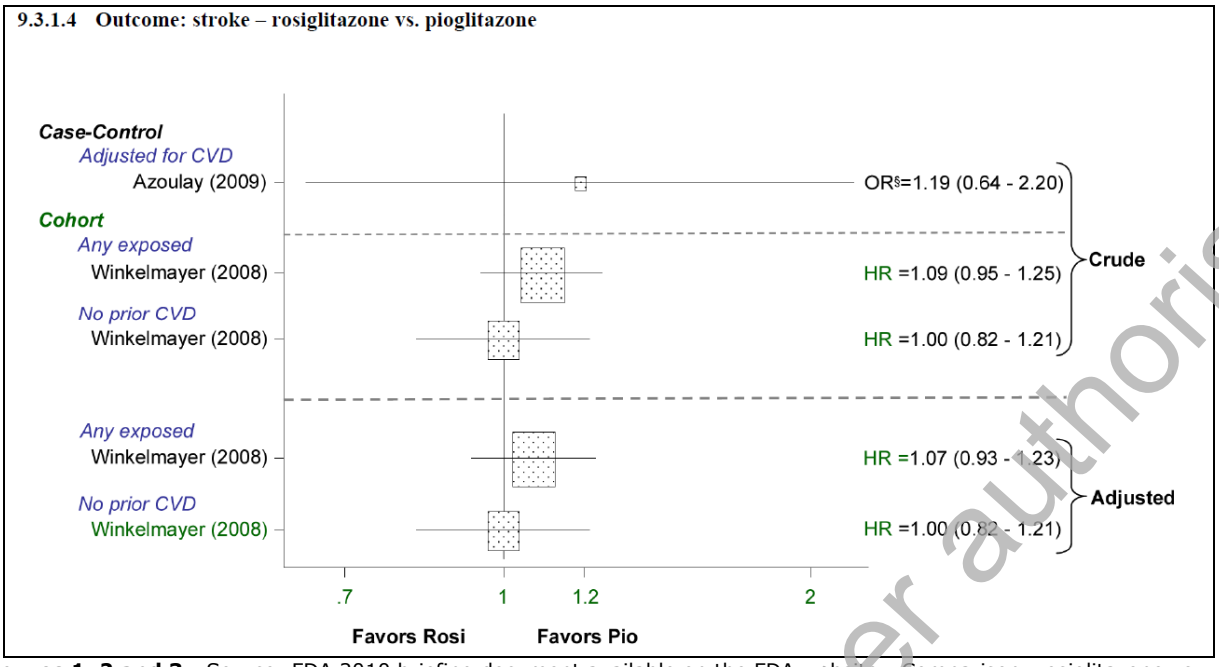

Figures 1, 2 and 3 - Source: FDA 2010 briefing document available on the FDA website - Comparison: rosiglitazone vs. pioglitazone (including combination therapy)

The MAH comprehensively reviewed the literature on observational cardiovascular studies published since June 2007 in which rosiglitazone was studied. A set of twenty-three studies which overlap with the studies included in the FDA's systematic review were identified, which were submitted to EMA as part of the appropriate PSUR submissions. Six of these studies were commissioned by the MAH and were discussed in the last renewal procedure. Twelve of the studies included a head to head comparison of rosiglitazone to pioglitazone for the outcome of myocardial infarction. Studies with lower variance of estimate and tighter confidence intervals had risk ratios very close to one, indicating no difference in the risk of myocardial infarction between rosiglitazone and pioglitazone. Four studies (Hsiao et al, 2009 (see reference 8.); Dormuth et al (see reference 9.), 2009; Stockl et al (see reference 10.), 2009 and Brownstein et al, 2010 (see reference 11.)) had wide confidence intervals reflecting low precision of the risk ratio estimates while three studies (Gerrits et al (see reference 12.), 2007; Brownstein et al, 2010 (see reference 11.) and Ziyadeh et al, 2009 (see reference 13.)) indicated a statistically significant increased risk for myocardial infarction with rosiglitazone compared to pioglitazone.

The CHMP noted the FDA review of observational studies including 21 studies examining cardiovascular endpoints in patients treated with rosiglitazone or pioglitazone as well as the MAH analysis. The CHMP also noted the FDA caution against the interpretation of results that include different measures of effect or different study designs. A number of studies resulted in a HR for MI above 1 (favouring pioglitazone), but for the majority of the studies the confidence intervals crossed unity. However, some studies showed a statistically significant increased risk of MI. Two studies based on elderly patients (Juurlink et al, Winkelmayer et al) showed a statistically increased risk of CHF and all-cause mortality associated with rosiglitazone, but no increased risk of MI, i.e. similar results as in the Graham et al study.

Bilik et al, Thiazolidinediones, cardiovascular disease and cardiovascular mortality: translating research into action for diabetes (TRIAD), published online: 17 MAY 2010, Pharmacoepidemiology and Drug Safety

The authors compared cardiovascular death (CVD) incidence, CV, and all-cause mortality in type 2 diabetic patients treated with either rosiglitazone or pioglitazone to determine whether rosiglitazone and pioglitazone have different CVD risks. The study analyses of survey, medical record, administrative, and National Death Index (NDI) data from 1999 through 2003 from Translating Research Into Action for Diabetes (TRIAD), a prospective observational study of diabetes care in managed care. Medications, CV procedures, and CVD were determined from health plan (HP) administrative data, and mortality was from NDI. Adjusted hazard rates (AHR) were derived from Cox proportional hazard models adjusted for age, sex, race/ethnicity, income, history of diabetic nephropathy, history of CVD, insulin use, and HP. Across TRIAD, 1,815 patients (24%) filled prescriptions for a TZD, 773 (10%) for only

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rosiglitazone, 711 (10%) for only pioglitazone, and 331 (4%) for multiple TZDs. In the seven HPs using both TZDs, 1,159 patients (33%) filled a prescription for a TZD, 564 (16%) for only rosiglitazone, 334 (10%) for only pioglitazone, and 261 (7%) for multiple TZDs. For all CV events, CV, and all-cause mortality, the authors found no significant difference between rosiglitazone and pioglitazone. The main results are summarised below in Table 3.

Table 2. Unadjusted adverse cardiovascular events and mortality by treatment group

	All health plans ($N=10$)				Health plans with both TZDs on formulary ($N=7$)			
	Rosi[a] treated	Pio[b] treated	*p* value	Unadjusted relative risk of rosi *versus* pio	Rosi treated	Pio treated	*p* value	Unadjusted relative risk of Rosi *versus* Pio
N	773	711			564	334		
Nonfatal MI (%)	17 (2)	22 (3)	0.28	0.71	12 (2)	8 (2)	0.79	0.89
Coronary revascularization (%)	16 (2)	16 (2)	0.81	0.92	15 (3)	11 (3)	0.58	0.80
Nonfatal MI or coronary revascularization (%)	26 (3)	30 (4)	0.39	0.80	21 (4)	15 (4)	0.57	0.83
Nonfatal stroke (%)	19 (2)	13 (2)	0.40	1.34	16 (3)	8 (2)	0.69	1.18
Nonfatal MI, coronary revascularization, or nonfatal stroke (%)	44 (6)	42 (6)	0.86	0.96	36 (6)	23 (7)	0.77	0.93
CV mortality (%)	7 (1)	12 (2)	0.18	0.54	4 (1)	3 (1)	0.76	0.79
All-cause mortality (%)	14 (2)	19 (3)	0.26	0.68	10 (2)	9 (3)	0.35	0.66
Nonfatal MI or all-cause mortality (%)	31 (4)	38 (5)	0.22	0.75	22 (4)	16 (5)	0.52	0.81
Nonfatal MI, nonfatal stroke or CV mortality (%)	42 (5)	43 (6)	0.61	0.90	31 (6)	19 (6)	0.90	0.97
Nonfatal MI, nonfatal stroke or all-cause Mortality (%)	46 (6)	48 (7)	0.53	0.88	34 (6)	23 (7)	0.61	0.88
Nonfatal MI, coronary revascularization, nonfatal stroke or all-cause mortality (%)	54 (7)	55 (8)	0.58	0.90	42 (7)	29 (9)	0.51	0.86

[a]Rosiglitazone.
[b]Pioglitazone.

Table 3 - Source: Bilik et al, published online: 17 May 2010, Pharmacoepidemiology and Drug Safety

The CHMP considered that the observational study by Bilik at al published in May 2010, based on data from the period 1999-2003 (i.e. before the publication of the first Nissen et al meta-analysis and the subsequent media attention) did not confirm the findings of the Graham et al study. The CHMP noted that the study showed no differences between rosiglitazone and pioglitazone for any CV event but considered that important limitations including small study size and differences in baseline characteristics between the two groups meant that the power to detect a difference in risk was questionable. The CHMP considered that the findings could not be considered to add greatly to the available evidence.

Wertz et al. Risk of Cardiovascular Events and All-Cause Mortality in Patients Treated With Thiazolidinediones in a Managed Care Population. Circ Cardiovasc Qual Outcomes 2010:3

This retrospective cohort study compared the risks of acute myocardial infarction (AMI), acute heart failure (AHF), or all-cause death among pioglitazone- and rosiglitazone-treated patients in a managed-care population. 36 628 patients over 18 years of age, newly initiated on rosiglitazone or pioglitazone between January 1, 2001, and December 12, 2005, were included. Patients were excluded if they had <1 year continuous eligibility preindex or a preindex insulin claim. Primary endpoint was time to composite event of acute myocardial infarction (AMI), acute heart failure (AHF) or death among pioglitazone- and rosiglitazone-treated patients. The National Death Index database was accessed to obtain date of death for patients who died during the study period. Propensity score matching was used to control for potential confounders. The Cox proportional hazards model was used to evaluate effects of exposure to rosiglitazone and pioglitazone on time to event. A total of 36 628 patients (58% male; mean age, 54 years) were identified. Of the rosiglitazone-treated patients, 602 (4.16%) had an AMI, AHF, or death compared with 599 (4.14%) propensity score–matched pioglitazone-treated patients. The main results are summarised below in Table 4.

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Cox Proportional Hazards Models for Risk of Composite Event of Interest (AMI or Acute Heart Failure or All-Cause Mortality)

	Hazard Ratio (95% CI)	*P* Value
Primary analysis		
Matched patients	1.03 (0.91–1.15)	0.666
Age 65+y	0.97 (0.83–1.12)	0.643
All patients	1.00 (0.90–1.11)	0.981
Patients were excluded 60 days after the end of index therapy		
Matched patients	0.97 (0.74–1.26)	0.823
Age 65+y	0.86 (0.61–1.21)	0.390
All patients	0.87 (0.68–1.11)	0.264
Patients were excluded at the end of index therapy		
Matched patients	0.88 (0.64–1.20)	0.413
Age 65+y	0.69 (0.46–1.02)	0.072
All patients	0.75 (0.57–1.00)	0.053

Pioglitazone was the reference group.

Table 4 - Source: Wertz et al. Circ Cardiovasc Qual Outcomes 2010:3

The CHMP noted the results of the study by Wertz et al, 2010. No significant difference between treatment groups were observed between matched groups for risk of composite event; HR 1.03 (CI 0.91-1.15). Despite being a reasonably large and apparently well-conducted study, the findings were not particularly reassuring given that this was a relatively young population (mean age 54 years) who could be considered to be at reduced baseline cardiovascular risk and generally a lower risk population compared to the population which ordinarily received treatment with rosiglitazone in the EU. Of particular note was the relatively low number of cardiovascular events observed in this study and also that the diabetes severity indicators suggested that the population examined did not have severe diabetes. It is questionable whether this study was adequately powered to detect a difference in risk between rosiglitazone and pioglitazone given the low number of cardiovascular events. The CHMP therefore considered that this study did not add substantially to the accumulating evidence.

In conclusion, the CHMP acknowledged that observational studies are associated with several limitations mainly due to the lack of randomisation to the studied treatment which always results in residual confounding. Results from such studies should therefore in general be looked upon as hypothesis generating rather than as providing confirmation of relationships, unless the observed relative risk is very strong. The CHMP acknowledged that most of the observational data was derived from studies based on North American databases. However, the Committee was of the opinion that the results of some of the identified observational studies comparing rosiglitazone and pioglitazone indicate an increased risk of MI associated with rosiglitazone, while other studies in the elderly population instead identified an increased risk of CHF and all cause mortality. In conclusion, the CHMP therefore considered that the evidence from observational studies to some extent supported the possible increase in cardiovascular risks of rosiglitazone.

Meta-analyses

Nissen and Wolski, Rosiglitazone revisited. An updated meta-analysis of risk for myocardial infarction and cardiovascular mortality. Arch Intern Med published online June 28, 2010

Nissen et al. published a meta-analysis investigating the risk for myocardial infarction and cardiovascular mortality in subjects receiving rosiglitazone, as an update to their 2007 meta-analysis. The meta-analysis used similar methods to the original study but also alternative analyses to enable inclusion of trials with no CV events. The main objective of the study was to systematically review the

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effects of rosiglitazone therapy on MI and mortality (CV and all-cause). The authors searched MEDLINE, the FDA web site and the MAH clinical trials registry for trials published through February 2010. The pre-specified criteria for inclusion of trials required that studies had a randomised comparator group, a similar duration of treatment in all study groups, and more than 24 weeks of drug exposure. By using these criteria, 56 eligible trials were identified including 19509 and 16022 patients assigned to rosiglitazone and comparators, respectively. The majority were short-term, placebo controlled trials not designed to investigate CV effects, and so not adjudicated, with many studies carried out in subjects with diseases other than type II diabetes. The meta-analysis was a study-level analysis as the authors did not have access to patient-level data. Fifteen of the 56 trials did not report any MIs, while 20 did not report any CV mortality. The trials without events were not included in the primary pre-specified analysis but were included in an alternative analysis. The main results for MI and CV mortality are summarised below in Table 5.

Primary Analysis of Risk for Myocardial Infarction and Cardiovascular Mortality

Method	No. of Studies	Rosiglitazone Group	Control Group	Peto OR (95% CI)	P Value
Risk for Myocardial Infarction[a]					
Including RECORD trial[4]	41	159/17 258	136/14 449	1.28 (1.02-1.63)	.04
Excluding RECORD trial	40	95/15 038	80/12 222	1.39 (1.02-1.89)	.04
Risk for Cardiovascular Mortality[b]					
Including RECORD trial	26	105/13 672	100/12 175	1.03 (0.78-1.36)	.86
Excluding RECORD trial	25	45/11 452	29/9949	1.46 (0.92-2.33)	.11

Table 5 - Source: Nissen and Wolski, Arch Intern Med Published online June 28, 2010

The CHMP agreed that the results from the updated Nissen et al meta-analysis confirm and provide additional weight to the previous analysis and the similar results presented by the MAH and FDA in their previous meta-analyses (2007/2008) indicating an increased risk of cardiovascular disease associated with the use of rosiglitazone. It should also be noted that the Nissen et al analysis also included the long term studies DREAM, ADOPT and RECORD. Analyses with and without RECORD had a substantial effect on the HR for CV mortality, but a much smaller effect on the risk for MI which was still statistically significant. Overall, the CHMP considered the evidence from the Nissen et al study to be robust and contributing to the overall benefit-risk assessment of rosiglitazone.

FDA meta-analysis of short-term trials

At the July 13 and 14, 2010 Advisory Committee meeting, the FDA presented two separate and newly performed meta-analyses of rosiglitazone and pioglitazone clinical trials, with a primary endpoint of MACE (CV death, myocardial infarction or stroke) and using patient level-data. The rosiglitazone analysis comprised 52 studies and the pioglitazone analysis 29 studies. The analyses were stratified by study, with sub-analyses conducted assessing the sensitivity of results to type of comparator group or background study medication. The long-term studies RECORD and PROactive (PROspective pioglitAzone Clinical Trial In MacroVascular Events) were not included to avoid obscuring any potential short-term signal. For most of the clinical studies contributing data to the meta-analyses, cardiovascular events were not prospectively adjudicated as the studies were not designed for this purpose. The rosiglitazone meta-analysis consisted of more trials and patients than the pioglitazone meta-analysis but fewer MACE events (109 and 117, respectively). MACE events were distributed sparsely through the rosiglitazone studies with all but two clinical trials (Study 211 – NYHA class I & II heart failure population, and Study 521 – patients with T2D and established coronary artery disease) having fewer than 10 such events. The rosiglitazone meta-analysis had 81% of patients enrolled in the placebo controlled trial-group compared to 39% in the pioglitazone meta-analysis. The pioglitazone meta-analysis had proportionately more patients in the monotherapy trial-level group (49% compared to 32%) and fewer in the sulphonylurea add-on trial-level group (10% compared to 26%). Regarding patient characteristics, the distribution of patients by nominal trial duration differed between the meta-analyses. There were more rosiglitazone patients enrolled in trials between 2 and 6 months in duration (69%), followed by 6 months to 1 year (25%) and 1 and 2 years (5%). For the pioglitazone meta-analysis, the distribution of patients was more uniform across the different trial duration categories; 47% in trials between 2 and 6 months, 30% in trials 6 months to 1 year, and 24% in trials between 1 and 2 years. The patients in both meta-analyses had similar average age and body mass index (BMI).

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In the rosiglitazone meta-analysis there were slightly more males (59% compared to 55%) and a higher proportion (44%) of patients known to have been treated in USA (compared to 30% in the pioglitazone meta-analysis; 13% had region missing). Patients in the pioglitazone meta-analysis had treatment for on average 77 days longer (265 days compared to 188). Patients in both meta-analyses had on average had diabetes for a similar period of time, but patients in the pioglitazone meta-analysis were less likely to have received previous treatment (59% compared to 78%). An overview of the results is shown below in Table 6 and Table 7.

Meta-analysis	Endpoint	Comparator n (%)	Pioglitazone/ Rosiglitazone n (%)	Total n (%)	Stratified OR (95% CI)
Pioglitazone (N=)		5642	6132	11774	
	MACE	63 (1.1)	54(0.9)	117 (1.0)	0.83 (0.56, 1.21)
	CV death	18 (0.3)	22 (0.4)	40 (0.3)	1.18 (0.60, 2.34)
	MI*	33 (0.6)	31 (0.5)	64 (0.5)	0.91 (0.53, 1.53)
	Stroke	16 (0.3)	10 (0.2)	26 (0.2)	0.61 (0.24, 1.43)
	Heart failure	50 (0.9)	75 (1.2)	125 (1.1)	1.47 (1.01, 2.16)
Rosiglitazone (N=)		6956	10039	16995	
	MACE	39 (0.6)	70 (0.7)	109 (0.6)	1.44 (0.95, 2.20)
	CV death	9 (0.1)	17 (0.2)	26 (0.2)	1.46 (0.60, 3.77)
	MI*	20 (0.3)	45 (0.4)	65 (0.4)	1.80 (1.03, 3.25)
	Stroke	16 (0.2)	18 (0.2)	34 (0.2)	0.86 (0.40, 1.83)
	Heart failure	40 (0.6)	88 (0.9)	128 (0.8)	1.93 (1.30, 2.93)

Table 6 - Source: FDA 2010 briefing document, p. 563, available on the FDA website - Analysis of safety endpoints by meta-analysis

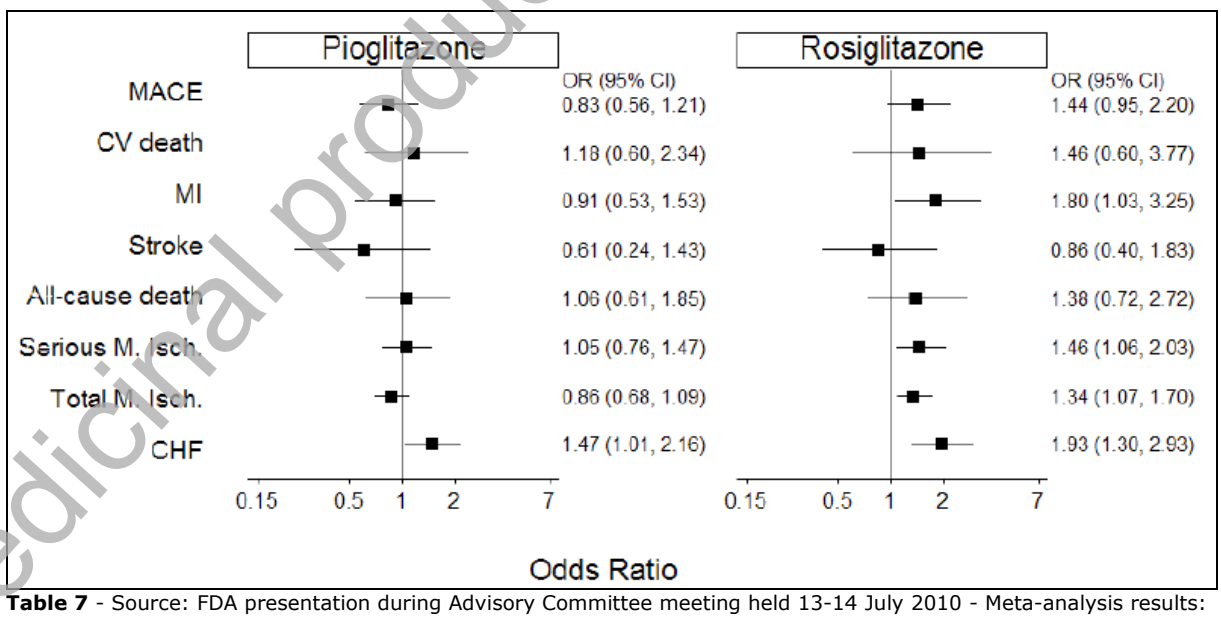

Table 7 - Source: FDA presentation during Advisory Committee meeting held 13-14 July 2010 - Meta-analysis results: Primary analysis set, all outcomes

The CHMP noted that the FDA meta-analyses was performed including short-term rosiglitazone and pioglitazone studies, with the majority not designed to assess CV outcomes. Trials were included in the meta-analyses if they were randomised, double-blind trials between 2 months and 2 years in duration,

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completed by December 2009 with targeted total daily dose for pioglitazone of 30 or 45 mg, and 4 or 8 mg for rosiglitazone with available patient-level data. The relevance of short term studies for the analyses of CV outcome measures needs to be considered in the context of the potential mechanism of the possible increased risk. If the mechanism is progression of atherosclerosis, this would probably not evolve within 3-6 months. If, on the other hand the mechanism is development of CHF, even short term studies may be of relevance.

The CHMP considered that the few cases of CV outcomes in the included studies and the differences between the rosiglitazone and pioglitazone studies included in the meta-analyses (treatment duration, number of events and design of the studies), make a direct comparison between the meta-analyses questionable. Despite this, the results of the two meta-analyses differed greatly: for the meta-analysis of the 52 rosiglitazone studies (16,995 patients), 109 MACE events were observed (i.e. 0.6%) while the meta-analysis of 29 pioglitazone studies (11,774 patients) reported 117 MACE events (i.e. 1.0%). The odds ratio (OR) for MACE was 1.44 (CI 0.95-2.20) for rosiglitazone and 0.83 (CI 0.56-1.21) for pioglitazone, although neither were statistically significant. For the individual components of MACE, the numbers of events were smaller. For CV death, the point estimate of the OR was above 1 for both rosiglitazone and pioglitazone, for stroke it was below 1, with wide confidence intervals for both. In the rosiglitazone meta-analysis, adverse events of myocardial infarction were more frequent than comparator (OR 1.80, CI 1.03-3.25) whereas for pioglitazone the OR was 0.91 (CI 0.53-1.53).

In conclusion, the CHMP considered that the rosiglitazone meta-analyses of short term studies show an increased HR for MI and MACE while this was not the case in the pioglitazone meta-analysis. Although the studies differ, the CHMP noted that for pioglitazone most HR are below 1, while the opposite was seen for rosiglitazone. The CHMP therefore considered that the evidence from meta-analyses presented contributed to the analysis of the cardiovascular risks of rosiglitazone and to its overall benefit-risk assessment.

Randomised clinical trials

RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes)

The RECORD study was prospectively designed to assess non-inferiority of rosiglitazone in combination with metformin or sulphonylurea compared with metformin and sulphonylurea dual therapy for CV outcomes. The primary endpoint was the time to first cardiovascular hospitalisation or cardiovascular death. The study employed a formal adjudication process for the blinded assessment of CV outcome and studied 4447 type 2 diabetic patients with a mean follow-up of 5.5 years. Despite a lower than expected event rate, the number of primary events (644) met the prospectively defined non-inferiority margin of 1.20. The upper limit of the 95 % confidence intervals for MACE (CV death, MI or stroke), all cause death and CV death were also below 1.2. Rosiglitazone showed an HR for heart failure of 2.10 (CI 1.35-3.27), and an HR for the secondary endpoint myocardial infarction of 1.14 (CI 0.80-1.63). Discontinuation of treatment resulted in 88% of patient-years' follow-up being on rosiglitazone. A pre-specified sensitivity analysis to test the stability of the primary endpoint to this effect (i.e. restricted to time on originally allocated dual therapy) yielded a very similar estimate for the HR (1.02) but, compatible with the smaller number of events included (500), a wider 95% CI (0.85-1.21). A further pre-specified sensitivity analysis was performed excluding events unlikely to be of atherosclerotic origin. This resulted in a HR of 0.97 and 95% (CI of 0.82-1.14). A total of 521 patients had incomplete follow-up for the primary endpoint, representing 7.2% missing patient-years experience (which was balanced between treatment groups). A total of 127 subjects (balanced between treatment groups), comprising 2% of maximum patient-years' follow-up that could have been achieved, had incomplete vital status follow-up.

PROactive (PROspective pioglitAzone Clinical Trial In MacroVascular Events) study

The PROactive study was a cardiovascular outcome study enrolling 5238 patients with type 2 diabetes mellitus and pre-existing major macrovascular disease, randomised to pioglitazone or placebo in addition to existing antidiabetic and cardiovascular therapy, for up to 3.5 years. The study population had an average age of 62 years; the average duration of diabetes was 9.5 years. Approximately one third of patients were receiving insulin in combination with metformin and/or a sulphonylurea. To be eligible patients had to have had one or more of the following: myocardial infarction, stroke, percutaneous cardiac intervention or coronary artery bypass graft, acute coronary syndrome, coronary artery disease, or peripheral arterial obstructive disease. Almost half of the patients had a previous myocardial infarction and approximately 20% had had a stroke. Approximately half of the study population had at least two of the cardiovascular history entry criteria. Almost all subjects (95%) were

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receiving cardiovascular medications (beta blockers, ACE inhibitors, angiotensin II antagonists, calcium channel blockers, nitrates, diuretics, aspirin, statins, fibrates). An overview of the results from both trials is shown below in Table 8.

	RECORD		PROactive*	
	Rosiglitazone (N=2220)	**MET/SU (N=2227)**	**Pioglitazone (N=2605)**	**Placebo (N=2633)**
Primary	321	323	514	572
	0.99 (0.85, 1.16)		0.90 (0.80, 1.02)	
All-cause mortality	136	157	177	186
	0.86 (0.68, 1.08)		0.96 (0.78, 1.18)	
MACE	154	165	257	313
	0.93 (0.74, 1.15)		0.82 (0.70, 0.97)	
CV death	60	71	127	136
	0.84 (0.59, 1.18)		0.94 (0.74, 1.20)	
Stroke (fatal or non-fatal)	46	63	86	107
	0.72 (0.49, 1.06)		0.81 (0.61, 1.07)	

Table 8 - Sources: MAH response document, Dormandy et al (2005) (see reference 14.); Wilcox et al (2007) (see reference 15.).

The MAH carried out further *post-hoc* analyses of the RECORD study following publication of the Graham et al paper, examining effects in the elderly population, for the primary endpoint, all-cause mortality, MACE and its components. The elderly were evenly distributed across the treatment arms with 577 patients aged 65 or above in the rosiglitazone group and 607 in the met/SU group. The underlying event rates were greater in the over-65s for both treatment groups, with the event rate for each major endpoint in the 65 or above group generally being at least double that in the under-65s. However, for the individual MACE component endpoints, the absolute number of events within each age group was relatively small. In the under-65 group, all hazard ratios were less than or close to 1, with confidence intervals including 1 for all endpoints except cardiovascular death. For cardiovascular death, the hazard ratio in the under-65s was 0.59 with a confidence interval excluding 1. In the over-65 age group the hazard ratio estimates were more variable across the endpoints, though in all cases the confidence intervals included 1. For the endpoints with relatively large numbers of events (primary outcome, all-cause death, MACE) the hazard ratios were close to 1. For components of MACE, results were more variable, with non-significant point estimates of 1.21, 1.39 and 0.72 for cardiovascular death, myocardial infarction and stroke respectively.

The MAH also discussed an indirect comparison of rosiglitazone and pioglitazone based on the RECORD and the PROactive studies, which provide long-term randomised and prospectively adjudicated cardiovascular outcome data. Both studies were agreed as post-authorisation commitment studies by EMA at the time of approval of the two drugs in 2000. The MAH highlighted the differences between these studies but noted that the only data the MAH had access to for the pioglitazone meta-analysis was that presented in the FDA briefing document.

The CHMP assessed the RECORD study in the variation EMEA/H/C/268/71. The CHMP concluded that the results did not change the benefit-risk balance for rosiglitazone and while information on RECORD was included in section 5.1 of the SPC, no changes to the warnings and precautions were considered to be warranted. Even though this was a long term RCT of cardiovascular endpoints, the study had limitations, such as the open label design (with blinded adjudication of CV events) and the choice of hospitalisation as a part of the primary endpoint, both factors that may potentially attenuate the ability of the study to show a difference between treatment arms. Concerning the analysis of the elderly in RECORD, sub-group analyses should be treated with caution, especially where the number of events is relatively small. However, considering that the elderly have an increased baseline risk of CV events compared to younger patients, an increased relative risk would translate into higher absolute risk in this population.

The CHMP noted the indirect comparison of the RECORD and PROactive studies performed by the MAH. However, the CHMP was of the opinion that the two studies differed in several key aspects, and any conclusions derived from such comparisons were considered to be of low relevance.

BARI-2D (Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes)

The BARI 2D study (see reference 16.) was an international, National Institute of Health-sponsored, cardiovascular outcomes trial which included 2,368 patients with T2DM and all patients had established

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ischemic heart disease. Patients were randomised to a diabetes treatment strategy (insulin-sensitization [IS] vs. insulin provision [IP]) and a coronary disease treatment strategy (prompt revascularization with intensive medical therapy vs. intensive medical therapy alone). The primary outcome was all-cause mortality and the principal secondary outcome was MACE (all-cause mortality, myocardial infarction or stroke). Patients assigned to the IS group were principally treated with MET and rosiglitazone and those assigned to the IP group with sulphonylureas, secretagogues, and insulin. With respect to use of rosiglitazone in the trial, at the three-year follow-up, 55% of patients in the IS group were taking rosiglitazone compared with 3% in the IP group. Rosiglitazone use was at the discretion of the treating clinician. The overall results showed no significant difference in the rates of death and major cardiovascular events between patients undergoing prompt revascularization and those undergoing medical therapy or between strategies of insulin sensitization and insulin provision. The BARI 2D Steering Committee performed post-hoc analyses to evaluate the cardiovascular safety of rosiglitazone among trial participants. This data was presented at the ADA in June 2010, and was also presented to the FDA Advisory Committee in July 2010. Patients who were treated with rosiglitazone had a higher baseline level of glycated haemoglobin (HbA1c), a longer duration of diabetes, more albuminuria, and were marginally younger than patients not treated with a thiazolidinedione. An overview of the results is shown below in Table 9.

Outcome	RR	P Value
Death	1.01 (0.72, 1.41)	0.97
MI	0.82 (0.58, 1.14)	0.24
Stroke	0.40 (0.18, 0.87)	0.02
Death/MI/Stroke	0.80 (0.63, 1.03)	0.08
CHF	1.16 (0.85, 1.58)	0.35

Table 9 - Source: Presentation by BARI-2D investigators during the American Diabetes Association 2010 Scientific Sessions, June 28th 2010 – Cardiovascular events with rosiglitazone during treatment plus 3 months vs. no TZD.

The MAH presented and discussed the results of BARI-2D (adjusted for baseline characteristics and other diabetes-related medications), noting the relative risk (RR) of less than one (and statistically significant for stroke and death/MI/stroke) with upper bounds for the associated 95% CI less than 1.2 for all outcomes except CHF where an RR of 1.16 (CI 0.85-1.58) was observed. The number of events recorded in this analysis (455 MACE events, 253 MI events) was approximately 4 times those recorded in the rosiglitazone FDA meta-analyses (109 MACE events, 65 MI events), reflecting the higher risk population in which the study was conducted compared to the low risk populations in studies from the meta-analyses.

The CHMP considered that the assessment of the results of the BARI 2 D study is complicated by the non-randomised allocation to rosiglitazone, and the fact that any post hoc analysis must be interpreted with care. Almost 1000 high-risk patients were exposed to rosiglitazone for almost 5 years in a study with prospectively adjudicated CV events, without evidence of increased risk of CV events (except for CHF, for which an increased RR of 1.16 (CI 0.85-1.58) was observed) compared to treatment with other antidiabetic agents. This contrasts with the results from the observational studies and the meta-analyses assessed above.

3.2. Usage patterns

The MAH consulted several, large, independent databases (IMS Midas, IMS Disease Analyzer, Cardiomonitor and Diabetes Dynamics) to analyse the usage patterns of rosiglitazone within Europe and individual EU member states. The databases either directly quantify pack or tablet sales to retail and hospital pharmacies, or collate prescription data from both generalists and specialists providing a representative view of practice patterns and prescribing dynamics for diabetes medication. Whilst methodology and data gathering may differ, the data is gathered electronically from a syndicated sample of physicians per country and these data are projected to national populations to provide estimates of actual usage. The MAH provided summary data on the current usage patterns for

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rosiglitazone and the fixed-dose combinations (FDCs) across EU and in member states, on usage patterns of specific interest, relative proportions of new patient initiations vs. repeat prescriptions, usage by age and usage in patients with increased CV risk. The data shows that 70% of rosiglitazone usage occurs within the G5 EU countries (UK, France, Germany, Italy and Spain), which all showed a consistent decline in rosiglitazone prescriptions since labelling restrictions were introduced in 2008, with the exception of Italy, which contributes by 8.5% to total tablet sales in EU. Countries such as Bulgaria, Croatia, Czech Republic, Estonia and Romania have also shown increased usage, but at negligible levels (approximately 1%) relative to rest of EU.

The MAH provided data on the usage patterns of rosiglitazone-containing tablets (Avandia, Avandamet (rosiglitazone + MET) and Avaglim (rosiglitazone + glimepiride) in totality and as individual formulations from March 2006 to 2010 in the EU. These data are sourced from the IMS Midas database collating wholesaler sales to pharmacies across Europe. Data from Cardiomonitor for G4 markets (excluding Spain), June 2010, suggests the majority of rosiglitazone usage appears to be as dual therapy (predominately with MET; 65%), the remainder as triple therapy (25%). Avandamet (rosiglitazone + MET FDC) seems to be the most commonly prescribed formulation (>70%), with a lesser use of Avandia (<20%) added to other OADs. The use of rosiglitazone with sulphonylureas (as dual therapy) and insulin appears negligible (0.01% and <0.01% respectively). Usage of rosiglitazone as monotherapy was also limited (approximately 10%). Data retrieved from IMS Disease Analyzer from July 2006 to March 2010 indicate a consistent decline in repeat prescriptions and proportionately very few new patient initiations on rosiglitazone-containing products. Most of the residual usage occurs in existing patients receiving repeat prescriptions, though this number is also declining. According to two independent data sources (Cardiomonitor and Diabetes Dynamics), between 55- 68% of rosiglitazone usage appears to be in patients under 65 years. The data suggest there is declining use in patients with IHD and a consistently very low usage in diabetic patients with reported CHF. The available data on usage patterns and patient demographics suggests the majority of patients receiving rosiglitazone are repeat prescriptions of Avandamet for moderate duration T2DM requiring a combination of 2 or 3 agents to maintain glycaemic control, with low levels of IHD or CHF.

The MAH also provided a summary of the rosiglitazone use in monotherapy, dual or triple combination oral therapy regimens for the treatment of T2DM. Data obtained from Cardiomonitor on patient cases (collected electronically quarterly from 600-800 generalists and specialists per country for G4 markets) indicate that most of the usage (65%) is as dual therapy with metformin followed by triple therapy (25%). Of this, most combination therapy is achieved through use of Avandamet, while usage of rosiglitazone as monotherapy is comparatively low (10%). The MAH provided patient-level data for 3 major G5 markets: France, Germany and the UK including prescribing dynamics (new initiation and repeat prescriptions) at 6 month intervals from September 2006 to March 2010. A trend line for 'net gains vs. losses' of patients prescribed rosiglitazone-containing products (*i.e.* new prescriptions minus patient discontinuations) was provided, based on data from IMS Disease Analyzer, a longitudinal patient database maintained by IMS Health collecting monthly patient data from GPs and specialists (approximately 2,000 physicians in total). Data are changes in absolute, non-projected patient numbers from sample physician sites per country contributing to the database. The MAH also provided a summary of rosiglitazone usage in patients older than 65 years, showing that between 33 and 46% of rosiglitazone usage occurs in patients over 65 years of age. Finally, the MAH analysed Cardiomonitor, a database enriched with patients with known CV risk factors, to derive an estimate of rosiglitazone prescribing patterns between June 2008 and June 2010 in patients with T2DM and known IHD or CHF. A summary of data sourced using the limited search terms available in the database (ischaemic heart disease; angina pectoris; unstable angina, myocardial infarction and heart failure) was presented, showing that rosiglitazone usage decreased by over 50% over 2 years (from 280 out of 5,958 patients in 2008 to 119 out of 5,964 patients in 2010). There was also a progressive decline in patients with T2DM and IHD treated with rosiglitazone, from 67 in June 2008 to just 20 in June 2010. Only 5 out of 119 patients with T2DM and CHF were prescribed rosiglitazone in June 2010. The overall trend shows a reduction in use of rosiglitazone and an associated steeper reduction in patients with IHD from 2008 to 2010.

The CHMP noted the data provided by the MAH regarding usage pattern and the impact of the current risk minimisation measures, utilising various databases. Despite the MAH claims that the data can be considered representative across the EU, there are clear limitations. Moreover, these data represent a sample of prescribing patterns across major markets, which may obscure variations within and across individual countries. Overall in the EU, rosiglitazone usage shows a decline after 2008 (with the exception of Italy and some eastern European countries). Although some of the changes coincide with the update of the product information, changes in total pattern of use may not reflect the impact of the risk minimisation measures. Only changes in pattern of use in "at risk" groups (patients with diagnosed cardiovascular diseases, and the elderly) may be attributed to risk minimisation measures, since those

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measures are aimed to reduce the exposure among such patient groups. Data from two different databases were presented for the age distribution of rosiglitazone users. Data from the first database (361 patients, up to Dec 2008) shows 32% of the patients to be over 65 years old. More recent data from the second database (77 patients, up to June 2010) shows 46% of the patients older than 65 years. Looking at the data from the second database, it is worrying that up to half of the rosiglitazone users might be over 65 years old, especially because this group are at increased risk, or may have undiagnosed cardiovascular diseases. Using a relatively small database, a decline in rosiglitazone prescriptions in patients with diagnosed IHD and CHF is shown since 2008. The MAH concluded that this coincides with the warning and risk minimisation measures introduced in 2008. However, only the data between 2008 and 2010 is shown, and the trend before 2008 is unknown. For this reason, no direct conclusion can be made regarding the impact of the risk minimisation activities.

The CHMP noted the distribution of new patient initiators and repeat prescriptions in three major EU countries (France, Germany, and UK). A general decline in repeat patients is observed in all three countries. The proportion of new initiators remains low, although it does not follow a clear pattern. The "net patient gain estimate" stays negative in the recent years, which indicates a continuous decline in number of patients. The main decline, however, is observed before 2008, and can therefore not be considered to be correlated to the update of the product information. The CHMP concluded any causal relationship between prescription numbers and implementation of restrictions for use should be interpreted with care.

EMA study in cardiac profile of patients using rosiglitazone-containing medicinal products

The EMA conducted a retrospective analysis of a cohort of patients prescribed rosiglitazone to measure the proportion of SPC non-conformers (patients with cardiac failure or history of cardiac failure and acute coronary syndrome) treated with rosiglitazone. The possible impact on exposure to the products of extending the contraindications to include other coronary ischaemic disorders beyond ACS was also analysed. The data was obtained from the UK GP database, THIN (The Health Improvement Network), which is representative of the general population in the UK and includes almost 9 million patients collected from over 430 GP practices. A number of limitations of the study were noted, including the absence of validation of the diagnoses of cardiac events, as well as the THIN data currently available to the EMA only covering a period up to November 2009, which makes it impossible to analyse any changes in prescribing patterns resulting from public debate on rosiglitazone over the last 10 months. Lastly, only UK patient data is available in THIN.

The total number of patients using rosiglitazone was analysed and the proportion of patients who were prescribed rosiglitazone despite having a contraindication (cardiac failure or ACS) between April 1, 2008 (entry into force of the additional cardiac contraindications) and November 30, 2009 (cut-off date for available data in THIN). The analyses were then repeated restricting to only cardiac failure contraindications (and not ACS). Since this contraindication was stated at the time of authorisation of rosiglitazone, the time window for this calculation was extended back to July 2000 (authorisation date for Avandia). Lastly, the analyses were repeated with an extended list of coronary medical terms – including both the current contraindications and non-contraindicated terms. This analysis was again restricted to the period April 1, 2008 to November 30, 2009.

Despite the limitations of the study, the CHMP considered that the results give an indication of how rosiglitazone is being used in the real-life setting. The results suggested that contraindications are not rigorously applied, as approximately 8% of patients using rosiglitazone are SPC non-compliers (having or having had a cardiac contraindication). A further 9% of patients have ischaemic coronary disease of a kind not currently contraindicated. If the presence of any cardiac ischaemic event can be regarded as constituting a risk factor then the proportion of patients at risk may be nearer to one in 6 (16.8%).

3.3. Risk minimisation activities

The MAH provided details of risk minimisation and management strategies to EMA as part of the Risk Management Plans submitted with the RECORD study variation (approved March 2010). Since the update of the product information in March 2008, the MAH has made a sustained effort to educate and build awareness about the PI and the patient profile in whom rosiglitazone may be used most effectively, through advisory boards with external experts on how to best communicate the appropriate usage of rosiglitazone and the sponsorship of scientific symposia on treatment paradigms in type 2 diabetes, including presentations on the benefits and risks of rosiglitazone during the European Association for Study of Diabetes (EASD) annual meetings. Educational materials on the updated PI,

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diabetes and CVD and the appropriate patient selection for use of rosiglitazone have been consistently made available at MAH exhibit areas at diabetes congresses.

In its written answers, the MAH considered that the new data available since the 2010 CHMP renewal opinion does not warrant any further modification to the current PI in Europe and was of the view that the data on patient use confirmed that EU physicians are prescribing rosiglitazone appropriately. Therefore, the MAH did not believe that restriction of use to specialists only is warranted. The MAH stated that they will continue to communicate the appropriate use of rosiglitazone to physicians in accordance to approved PI. Following the preparatory extraordinary CHMP, the MAH revised its initial position, and discussed further potential risk minimisation measures during the September 2010 CHMP oral explanation, in particular changes to the legal status to restricted medical prescription and restriction of the indication to use with metformin only.

The CHMP noted the initial MAH position that no further risk minimisation measures are necessary to maintain a positive safety profile for rosiglitazone. The CHMP considered that the exposure data provided by the MAH show that prescription of rosiglitazone is rapidly decreasing in virtually all EU countries. Clinical experts witness that most formularies and clinical guidelines state the warnings associated with the use of rosiglitazone. Given the high rates of co-morbidities in patients that could benefit from rosiglitazone, the CHMP is of the opinion that this is the maximally achievable level of risk minimisation, and it is unlikely that any further risk minimisation activities could change the current status. The CHMP maintained this position when considering the additional risk minimisation measures discussed by the MAH during the September 2010 CHMP oral explanation. The CHMP was of the opinion that these could not practically or realistically be implemented.

TIDE (Thiazolidinedione Intervention With Vitamin D Evaluation)

Following the 2007/2008 benefit-risk assessment, the CHMP required the MAH to commit to undertake a large, multicentre controlled clinical trial, the TIDE (Thiazolidinedione Intervention With Vitamin D Evaluation) trial. The MAH collaborated with the Academic Research Institute, Population Health Research Institute (PHRI) on the selection of countries suitable for the TIDE trial, based on past experience of running clinical trials, including large cardiovascular outcomes studies. PHRI identified and worked with National Leaders from each of the countries to evaluate the enrolment capabilities based on the TIDE inclusion/exclusion criteria. As a result, it was agreed to initiate between 800-850 sites to recruit TIDE. The MAH presented the geographical distribution of TIDE study sites and patient enrolment as of July 2010, with the first site initiated in May of 2009 in North America, 1332 patients having been randomised out of a total of 2,327 patients screened, with an average rate of enrolment of 84 patients per week. The number of active sites increased to 355. The first site in Europe was initiated in December 2009. The rate of enrolment in Europe was on average 33 patients per week during July 2010. The TIDE study has an overall MACE event target of 1050 events. Assuming that approximately 60% of events occur on the TZD treatment arms, somewhere in the region of 630 events are expected for a comparison of rosiglitazone to pioglitazone. This would have at least 90% power to detect a 30% increase in hazard for one TZD compared to the other, or 80% power to detect a 25% increase. Therefore, based on the overall study event target, the MAH considered TIDE to be well-powered for MACE outcome, the most commonly used major composite event for cardiovascular outcomes studies, combining cardiovascular death, myocardial infarction and stroke. It is well recognised that powering a trial on an individual component of MACE is not feasible, due to the extremely low event rates, a problem compounded by the recent historical trend for MACE event rates to decrease. TIDE has allowed for this by using a conservative estimate of the MACE event rate of 2% per year. In order to power TIDE on a component of MACE, the trial size would need to be vastly in excess of 16,000 patients. For example, if a component of MACE occurred at a rate of just 1% per year, the sample size would have to double to 32,000 in order to maintain the same level of power - a trial that would be quite unfeasible to conduct. As with other outcomes studies, TIDE will conduct analyses of each component of MACE as secondary analyses. On July 21, following the FDA Advisory Committee meeting, the FDA placed the ongoing TIDE cardiovascular outcome study on partial clinical hold, meaning that no new patients may be enrolled into the trial until further notice from the FDA. Patients already enrolled in the trial will be allowed to continue to participate.

The CHMP noted the information provided by the MAH, including the placing of the study on partial hold by FDA. The CHMP discussed whether the TIDE study can provide valuable information regarding the cardiovascular risk associated with rosiglitazone and the committee agreed that the study was adequately powered to detect a 25% increase in overall MACE event for one TZD compared to the other. The explanation that it is not feasible to power the trial on an individual component of MACE, due to the low event rates and the commitment of the MAH to conduct analyses of each component of MACE as secondary analyses was endorsed. However, due to slow recruitment and the fact that the

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trial is on hold, the CHMP seriously questioned whether the TIDE study will be able to provide the expected information.

Consultation of Scientific Advisory Group

At the request of the CHMP, a Diabetes/Endocrinology Scientific Advisory group (SAG) meeting was held on 19 July 2010. The SAG felt that the new data on rosiglitazone did strengthen the concerns about possible cardiovascular risk with rosiglitazone. Despite the acknowledged shortcomings of meta-analyses and observational studies, both the updated Nissen et al meta-analysis and the Graham et al study reinforced the signal of increased CV events. The final RECORD data was considered to provide partial reassurance only, reinforcing concerns regarding CHF. Overall, the SAG felt that the advance in knowledge was incremental, but also that the balance had shifted further against rosiglitazone. Regarding differences in CV risk between rosiglitazone and pioglitazone, the SAG noted the lack of head-to-head comparisons. The meta-analyses performed for rosiglitazone and pioglitazone separately do however favour pioglitazone in outcomes such as MACE and MI, but not with respect to CV death. Concerns were expressed about the cardiovascular safety of the TZD class as a whole, in particular with regard to CHF, which could be a manifestation of ischaemic damage as well as of fluid retention. Overall, the SAG felt that there was no evidence to support any cardiovascular advantage of rosiglitazone. The lack of a mechanistic basis for any difference between the two TZDs made it particularly difficult to adjudicate the conflicting clinical evidence. Regarding the appropriate place in therapy for rosiglitazone, there was general agreement that rosiglitazone offers no unique benefit over pioglitazone. Given the similarity of the two agents in terms both of efficacy and non-cardiovascular safety, no subgroup(s) more suitable for rosiglitazone could be identified, although the possibility that rosiglitazone might be used in patients with a better CV safety profile, e.g. a younger population while excluding those with longstanding diabetes, was discussed. The SAG was unconvinced as to the efficacy or practical implementation of current risk minimisation measures, other than exclusion of those with a history of heart failure. Since the effectiveness of the previously implemented measures was unclear, it was not possible to estimate the impact of any future measures. The SAG also discussed the feasibility of excluding patients at increased CV risk, taking into account that all patients with type 2 diabetes fall into this category, as well as the possibility to restrict use of rosiglitazone to secondary care, as proposed by the MAH during the oral presentation to the SAG. Since European guidelines for cardiovascular screening exist, it would be theoretically possible to devise such a schedule for patients considered suitable for rosiglitazone, although feasibility and cost would remain obstacles to practical implementation. However, the SAG considered that mandatory pre-prescription testing for ischaemic heart disease would represent a very high hurdle, especially since the drug would need to be withdrawn, should evidence of cardiovascular disease later appear. In addition, restriction to secondary care would run counter to the universal shift towards GP based prescribing for diabetes.

4. Overall discussion and benefit-risk assessment

Benefit

Patients with type 2 diabetes are known to be at increased risk of macro- and microvascular complications including cardiovascular morbidity and mortality and the main aim of using antidiabetic drugs is to reduce these risks. In addition to a clinically relevant reduction of glucose parameters, an oral anti diabetic agent (OAD) should preferably show at least neutral or beneficial effects on associated cardiovascular risk factors (e.g. obesity, blood pressure, lipid levels). Other important aspects include the incidence of hypoglycaemia and the impact on liver and renal function. Studies examining rosiglitazone monotherapy have demonstrated statistically significant and clinically relevant reductions in the surrogate efficacy marker 'mean HbA1c' (ranging from -0.8% to -1.5%) and fasting plasma glucose (ranging from -1.7 to -4.2mmol/L) versus placebo at 26 weeks. Rosiglitazone used as dual and triple oral therapy in combination with other OADs demonstrated additional reductions in HbA1c.

The CHMP noted that rosiglitazone has demonstrated glycaemic efficacy, with up to 1.5% reduction in HbA1c when used as monotherapy or in different combinations in short terms studies, without being associated with hypoglycaemia. In long-term studies of up to 5 years' duration, rosiglitazone has shown more durable glycaemic control compared to MET or SU. The durable glycaemic control has been associated with reductions in microalbuminuria, a proven marker of diabetic nephropathy. Furthermore there was no increase in microvascular complications in RECORD compared to MET and SU.

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Long term efficacy has been studied in 2 different trials. In ADOPT (median treatment duration of 4 years), in patients with a short treatment duration, rosiglitazone as monotherapy significantly reduced the risk of reaching monotherapy failure (fasting plasma glucose >10.0 mmol/L) by 63 % relative to glibenclamide (HR 0.37, CI 0.30-0.45) and by 32 % relative to metformin (HR 0.68, CI 0.55-0.85). In RECORD, at 18 months, rosiglitazone as add-on dual therapy to ongoing metformin or sulphonylurea treatment was non-inferior to the combination of sulphonylurea plus metformin for lowering HbA1c. Rosiglitazone has also been shown to reduce insulin resistance at the level of adipose tissue, skeletal muscle and the liver. Treatment is associated with a low incidence of hypoglycaemia and there is no need for dose adjustment in patients with mild and moderate renal insufficiency.

The CHMP also noted that direct data concerning the impact of rosiglitazone on the incidence of microvascular events (diabetes related, eye, foot, renal) are sparse. The development of microalbuminuria, which is one of the characteristic microvascular complications of diabetes and associated with increased CV risk, was examined in some rosiglitazone studies. In the ADOPT study, progression of urinary albumin creatinine ratio was significantly reduced with rosiglitazone treatment compared with metformin. However, the total number of microvascular events in the RECORD study was assessed and although the incidence was lower in the rosiglitazone group compared to metformin/sulphonylurea group, the difference was not significant: 59 (2.7%) vs. 78 (3.5%) subjects, HR 0.75 (CI 0.54-1.05). In rosiglitazone monotherapy studies, rosiglitazone has demonstrated beneficial effects on some of potential surrogate markers for risk of CVD such as C-reactive protein and has been shown to reduce carotid intima-media thickness (cIMT) relative to control in patients with type 2 diabetes. In the APPROACH study, the primary efficacy endpoint (change in percent atheroma volume) showed an increase in the glimepiride group (adjusted mean 0.43; SE 0.331) and a decrease in the rosiglitazone group (adjusted mean -0.21; SE 0.331). The difference, however, was not statistically significant (mean -0.64, CI -1.457-0.173). Rosiglitazone has also been examined in patients with NASH (non alcoholic steatohepatitis) and has been shown to improve steatosis and transaminase levels.

Risk

Observational studies
The study by Graham et al, based on an elderly population, showed that HRs for stroke, heart failure, all-cause mortality, and the composite consisting of AMI, stroke, heart failure, or all-cause mortality (HR 1.18, CI 1.12-1.23) were increased for rosiglitazone compared with pioglitazone. The adjusted HR for MI was not significantly increased (HR 1.06, CI 0.96-1.18).

The FDA performed a review of observational studies including 21 studies examining CV endpoints in patients treated with rosiglitazone or pioglitazone. Nine studies comparing rosiglitazone and pioglitazone were identified, while the MAH added 3 additional studies to their own analysis. Most studies resulted in HR for MI above 1 (favouring pioglitazone), but for the majority of the studies the confidence intervals crossed unity. Studies with lower variance of estimate and tighter confidence intervals had risk ratios that were very close to one, indicating a very small risk increase. Furthermore, similar bias may be applicable to all studies (e.g. different patient populations due to media attention after 2007) explaining the consistency of the results between the studies. However, a number of studies showed a statistically significant increased risk with rosiglitazone. Two studies based on elderly patients (Juurlink et al, Winkelmayer et al) showed a statistically increased risk of CHF and all-cause mortality associated with rosiglitazone, but no increased risk of MI.

The findings of an increased risk of some CV events for rosiglitazone compared to pioglitazone were not confirmed in a study by Bilik et al, where no pattern of clinically meaningful differences in CV outcomes for rosiglitazone- versus pioglitazone-treated patients (all HR very close to 1) was observed. The CHMP noted important limitations including small study size and differences in baseline characteristics between the two groups which meant that the power to detect a difference in risk was questionable. The CHMP considered that the findings of this study could not be considered to add greatly to the available evidence.

Similar results were found in a data base study by Wertz et al. Primary endpoint was time to MI, acute heart failure or death. No difference between treatment groups were found for the risk of composite events (HR 1.03 with CI 0.91-1.15). It was noted that the number of cardiovascular events observed in this study was relatively low and that the diabetes severity indicators suggested that the population examined did not have severe diabetes and the CHMP questioned whether this study was adequately powered to detect a difference in risk between rosiglitazone and pioglitazone. The CHMP considered that the findings of this study could not be considered to add greatly to the available evidence.

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The CHMP acknowledged the limitations of observational studies (mainly due to the lack of randomisation to the studied treatment, which always results in residual confounding). However, the CHMP was also of the opinion that observational studies may better reflect the real life situation than randomised clinical trials and therefore decided to take into consideration the results from the available observational studies.

Meta-analyses

The Nissen et al meta-analysis initially published in 2007 was updated and published on 28th June 2010 to include 56 studies. The risk for MI was 1.28 (CI 1.02-1.63) and the risk for CV mortality was 1.03 (CI 0.78-1.36). This analysis also included the long term studies DREAM, ADOPT and RECORD. It is noteworthy that RECORD had a substantial effect on the HR for CV mortality (risk for CV mortality excluding RECORD 1.46 (0.92-2.33) but a much smaller effect on the risk for MI (risk for MI excluding RECORD 1.39 (CI 1.02-1.63), although still statistically significant.

The CHMP assessed the results of several meta-analyses performed using rosiglitazone studies. The FDA performed a meta-analysis in 2007 which was recently updated to include 52 short term studies. The results showed an odds ratio compared to comparators of 1.44 (CI 0.95-2.20) for MACE and 1.80 (CI 1.03-3.25) for MI. Even though the number of events was limited, the performed sub-analyses based on background therapy and comparators were considered to be of limited value.

The FDA also performed a meta-analysis of 29 pioglitazone studies. The odds ratio was 0.83 (CI 0.56-1.21) for MACE, and 0.91 (CI 0.53-1.53) for MI compared to comparators. The HR for CHF was above 1 and statistically significant for both rosiglitazone and pioglitazone.

The CHMP noted the limitations of these meta-analyses, such as the inclusion of studies not designed to look at CV events and the low number of events and that the study populations in the included studies may not reflect the restrictive EU SPC but nevertheless considered that the studies add to the mounting evidence of increased risk cardiovascular outcomes of rosiglitazone.

Long term randomised controlled trials

The only prospective study designed to assess CV outcomes is the RECORD study in which non-inferiority was reached for the primary endpoint (CV hospitalization or death) compared to metformin/sulphonylurea (HR 0.99, CI 0.85-1.16). The HR was 1.14 (CI 0.80-1.63) for fatal and non-fatal MI, 0.84 for CV death (CI 0.59-1.18) and 0.93 (CI 0.74-1.15) for MACE. Patients had a mean duration of disease of 6-8 years and approximately 15% had previous or current IHD.

In the BARI 2 D study, the allocation to rosiglitazone was non-randomised. The RR for MACE and MI were 0.80 (CI 0.63-1.03) and 0.82 (CI 0.58-1.14), respectively compared to patients not treated with a TZD. Even though the assessment of the results of the BARI 2 D study is complicated by the non-randomised allocation to rosiglitazone, almost 1000 high-risk patients were exposed to rosiglitazone for almost 5 years in a study with prospectively adjudicated CV events, without evidence of increased risk of CV events, except for CHF where a RR if 1.16 (CI 0.85-1.58) was observed. These results stand to some extent in contrast to the results of the meta-analyses and observational studies.

The ADOPT study was not designed to evaluate cardiovascular endpoints and there was no separate adjudication of CV events, nor were patients followed for assessment of CV events after their withdrawal from treatment. The HR for ischemic adverse events was not increased compared to metformin but slightly increased compared to sulphonylurea, although not statistically significant (HR 0.99 (CI 0.76-1.30) and 1.18 (CI 0.88-1.57), respectively). The study included drug naive subjects recently diagnosed (≤3 years) with type 2 diabetes.

The DREAM study (see reference 17.) included patients with impaired fasting glucose and/or impaired glucose tolerance in examining prevention of type 2 diabetes. CV outcomes were adjudicated, but event rates were low. The evaluation of the 'any CV event' composite endpoint (consisting of MI, stroke, CV death, revascularization, CHF and angina) resulted in a HR of 1.37 (CI 0.97-1.94). However, the main difference concerned the incidence of heart failure.

Other safety concerns

The CHMP also noted the other safety concerns associated with the use of rosiglitazone. It has been known since the time of approval that treatment with rosiglitazone can lead to fluid retention. Peripheral oedema is a common adverse event (reported more often in women than in men; 3- 5.1% and 1-1.5 % in women and men, respectively). A dose-dependent increased incidence of congestive heart failure has also been observed when rosiglitazone was added to treatment regimens including

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sulphonylurea or insulin (incidence 2.4%, compared to 1.1% with insulin alone). In the RECORD study, the HR for heart failure was 2.10 (CI 1.35-3.27) compared to comparators. Weight gain is also a well known adverse event. In the ADOPT study, patients treated with rosiglitazone experienced a mean weight gain of 4.8 kg over a period of 5 years. The mechanism is most likely attributable to both fluid retention and increased fat mass. Anaemia is reported as a common adverse event, most likely as a result of haemodilution. Cases of new onset and worsening diabetic macular oedema in patients receiving rosiglitazone have been observed in post-marketing reports, but were not reported in the ADOPT study. An increased risk of distal bone fractures in females first identified in ADOPT (HR 2.13 and 1.81 compared to SU and MET, respectively) was also observed in the RECORD study.

Benefit-risk balance

The CHMP noted that rosiglitazone is associated with a glucose reducing effect similar to other OADs and a mechanism unique to the TZD class which increases insulin sensitivity, but also with adverse events such as associated fluid retention as well as an increased risk of bone fractures which limits its place in the treatment of patients with type 2 diabetes. However, for patients treated according to the currently approved SPC, in particular patients intolerant to metformin, patients with severe impairment of insulin sensitivity and patients for whom hypoglycaemia would be a relevant problem with other treatment alternatives, the benefits have until recently been considered to outweigh the risks, provided that the warnings and contraindications in the product information are adhered to. During the recent years, accumulating data has emerged that increasingly indicated an increased risk of IHD for rosiglitazone compared to other comparators. These data have already been assessed by the CHMP and the target population for rosiglitazone has been restricted (contraindication for all degrees of CHF and warnings concerning patients with current or previous IHD).

In the current benefit-risk assessment, the CHMP considered in particular the newly available data but took into account the entire body of available data. Antidiabetic drugs should preferably reduce the risk of ischaemic heart events or at least be neutral in this respect. However, based on the data accumulated over time since the initial authorisation, the CHMP concluded that rosiglitazone puts patients at risk for increased cardiovascular harm. The CHMP considered that the new data made available since its opinion on the renewal in March 2010 (i.e. the updated meta-analysis by Nissen et al, the Graham et al study and the FDA meta-analysis) strengthens the association between rosiglitazone and an increased risk of cardiovascular outcomes (in particular myocardial infarction and congestive heart failure). The report of the Diabetes/Endocrinology Scientific Advisory group and the EMA analysis of rosiglitazone usage based on the THIN database were also taken into account in the assessment.

Although the magnitude of the observed increased cardiovascular harm associated with rosiglitazone use is modest, depending on the data analysed, it can potentially translate into an absolute risk increase of importance. Considering that, by definition, all patients with type 2 diabetes mellitus who could benefit from rosiglitazone treatment have an increased risk of IHD, it is therefore impossible to identify a true low risk population and it is of particular concern that the effectiveness of the current risk minimisation measured is questioned. The CHMP also noted the SAG position that no further realistic risk minimisation measure could be identified that would reduce the risk associated with rosiglitazone in particular in a primary care setting, and that therapeutic alternatives are available due to new classes of drugs having entered the market since the initial authorisation. Rosiglitazone does not demonstrate clear clinical benefits to balance its increased risk of cardiovascular outcomes and does not provide any unique advantages. As no further realistic risk minimisation measures could be identified, the CHMP was therefore of the opinion that the overall benefit-risk balance for rosiglitazone is no longer positive.

5. Overall conclusion

Having considered the overall submitted data provided by the MAH in writing and during the oral explanations, the CHMP concluded that in view of the increase risk of cardiovascular outcomes and as no further realistic risk minimisation measures could be identified, the overall benefit-risk balance for rosiglitazone is no longer positive.

The CHMP, having considered the matter, recommended the suspension of the marketing authorisations for Avandia, Avandamet and Avaglim.

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6. Communication plan

As part of this procedure, the MAH and the CHMP agreed the wording of a 'Dear Healthcare Professional Communication' designed to inform prescribers and pharmacists of the outcome of the Article 20 review. Following the CHMP recommendations, the MAH provided a communication plan which is detailed below. The MAH will distribute the DHPC letter to physicians (including primary care physicians, diabetologists, cardiologists and internal medicine specialists) and pharmacists as per the below timetable.

Date	Action
20th September	CHMP/EMA verbal debriefing with GSK following OE
21st September	GSK / CHMP agree content of DHCP letter
23rd September	GSK translation of agreed letter
24th September	Member States agree translations
Week of 27th September	GSK initiates distribution of letter

The MAH will initiate distribution of the DHCP letter by post as translations are approved by member states, but not prior to EMA press release. The MAH will also post the DHPC (in English only) on its website, along with the MAH press release and contact information. A Dear Investigator Letter will be distributed to those EU investigators and agencies participating in TIDE during the week of 27th September informing them of the CHMP opinion.

7. Conclusion and grounds for the recommendation

The Committee reviewed in particular the newly available data but took into account the entire body of available data, including the report of the Diabetes/Endocrinology Scientific Advisory group and the EMA analysis of rosiglitazone usage obtained from the THIN database.

The Committee reiterated the CV safety concerns with regards to rosiglitazone which led to the current SPC restrictions in patients with ischaemic heart disease such as the contra-indication for patients with acute coronary syndrome (ACS), the warning stating that rosiglitazone may be associated with an increased risk of myocardial ischaemic events and the precaution that rosiglitazone should not be used in patients with myocardial ischaemic symptoms. In addition the CHMP noted that the use of rosiglitazone is associated with a number of identified adverse events (PPAR-gamma-associated fluid retention including heart failure, weight gain, anaemia, macular oedema and bone fractures).

The Committee considered that the new data made available since its opinion on the renewal of Avandia in March 2010 (including the Graham et al study, the Nissen et al study and the FDA meta-analysis) significantly strengthen the association between rosiglitazone and an increased risk of cardiovascular outcomes (including myocardial infarction and congestive heart failure).

The Committee is of the opinion that the new data made available since its opinion on the renewal of Avandia in March 2010, in addition to the already accumulated data derived from randomised clinical trials, observational studies, meta-analyses and spontaneous reports, impacts the risk profile of rosiglitazone negatively.

The Committee considered that no further risk minimisation activities could be identified which would be expected to reduce the risks of Avandia, Avandamet and Avaglim to an acceptable level or predict which patients may be at risk, taking into account the restrictions and warnings already in place.

The Committee concluded, in view of available data, that the risks associated with the use of rosiglitazone in the treatment of type 2 diabetes mellitus outweigh its benefits.

The Committee, as a consequence, took the view that the benefit-risk balance of rosiglitazone is not positive under the normal conditions of use.

The Committee has therefore recommended the suspension of the Marketing Authorisation for Avandia, Avandamet and Avaglim until the conditions for lifting the suspension are fulfilled.

For the suspension to be lifted the MAH should provide the Committee with convincing and robust data to identify a patient population in which the clinical benefits of rosiglitazone-containing products clearly outweighs the risks.

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