

The rosiglitazone decision process at FDA and EMA. What should we learn?

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Abstract. In September 2010 the EMA decided to suspend the market authorisation of rosiglitazone, while the FDA decided to restrict the use of rosiglitazone. These actions were taken approximately 10 years after the introduction of rosiglitazone, because rosiglitazone might be associated with an increased risk of ischemic heart disease.

It is often stated that the first signs of an increased risk of ischemic heart disease were noticed in 2004, however already in 2001 the FDA concluded, based on data available to the EMA at the time of initial approval, that rosiglitazone should not be used in combination with insulin, because this combination therapy was associated with an increased risk of cardiac failure and ischemic heart disease.

Remarkably, in 2007, when the evidence against this combination therapy had increased, the EMA made a decision that encouraged the use of insulin in combination with rosiglitazone, while the FDA tried to restrict this combination therapy.

Despite the publication of several studies, including a large randomized controlled study, the cardiovascular risk of rosiglitazone still has not been definitively established.

The weight given to the benefits and the risks seems mainly a subjective decision. To prevent new cases like rosiglitazone, more attention should be given to evaluation of study protocols of safety trials prior to their starts.

This paper gives a critical overview of the decision making process at the FDA and the EMA on the basis of public available information.

Keywords: Rosiglitazone, FDA, EMA, decisions, myocardial ischemia

1. Introduction

Rosiglitazone (Avandia[®]) is a thiazolidinedione (TZD) antidiabetic agent which improves glycaemic control by improving insulin sensitivity. At the time of marketing authorisation in the European Union (EU) in March 2000, rosiglitazone usage was restricted to second-line oral combination therapy. An initial request for a monotherapy first-line indication in 1999 had been rejected by the scientific committee of the European Medicines Agency (EMA), mainly due to uncertainty about the cardiovascular safety profile [1]. In contrast, the US Food and Drug Administration (FDA) approved rosiglitazone in May 1999 for the treatment of diabetes type 2 as first-line monotherapy or in combination with metformin; rosiglitazone could become GlaxoSmithKline (GSK)'s second biggest selling drug [2, 3].

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In September 2010, about 10 years after the initial marketing authorisation, the EMA suspended the marketing authorisation of rosiglitazone in the EU, because the benefits of rosiglitazone no longer outweighed the risks [4].

In contrast, the FDA decided that rosiglitazone should not be withdrawn from the market. They decided that the use of rosiglitazone would be restricted within the confines of a Risk Evaluation and Mitigation Strategy (REMS) [5].

In the past years, a lot of issues regarding rosiglitazone have been discussed in the literature. However, an overview of the decision process, based on public available information, is lacking. In this review the decision process of the FDA and EMA will be discussed.

2. Initial authorisation of rosiglitazone

At the time of approval at the EMA, there were concerns about the association of rosiglitazone with anemia, weight gain, fluid retention, oedema and a potentially unfavourable effect on the lipid profile. Furthermore, the combination of rosiglitazone and insulin was associated with a clear trend to an increased incidence of congestive heart failure (CHF) [6].

In March 2000 the EMA only granted a second line indication as add-on to metformin or sulphonylurea [7]. An initial request for a monotherapy first-line indication had been rejected by the EMA in 1999, mainly due to uncertainty about the cardiovascular safety of rosiglitazone [1]. The EMA concluded that there was insufficient evidence of efficacy of rosiglitazone in monotherapy available [6].

It is remarkable that the FDA approved rosiglitazone in 1999 as first-line monotherapy since the EMA based their decision on similar data as the FDA.

3. Combination therapy of rosiglitazone and insulin

At the time of approval, rosiglitazone was in the EU contraindicated for heart failure or a history of heart failure, because preliminary data from clinical trials showed that combination of rosiglitazone with insulin was associated with a higher incidence of CHF in comparison with insulin alone [6]. Therefore, also a contraindication regarding combined use with insulin was added to the Summary of Product Characteristics of rosiglitazone in the EU [1].

In contrast, at the time of initial approval the FDA decided that contraindications regarding CHF and combination therapy with insulin were not needed. However, safety data from trials that evaluated the combination of rosiglitazone and insulin were not yet available [6, 8]. After these data became available, the US labelling was subsequently updated with a precaution regarding combined use with insulin [9].

In 2003 the FDA approved combination therapy of rosiglitazone with insulin for the treatment of patients with type 2 diabetes. In contrast, in 2001 the indication of combination therapy of rosiglitazone and insulin was not approved by the FDA, because the small improvements in the surrogate end points did not justify the increased risk of cardiac failure and other adverse cardiovascular events. For approval of combination therapy, the FDA reviewers stated that the manufacturer had to show in trials longer than 26 weeks long-term reductions in morbidity and mortality [10]. By 2003 such trials were not performed. The reviewers of the FDA concluded that patients treated with both rosiglitazone and insulin were at increased risk of cardiac events, but approved the combination treatment with rosiglitazone and insulin of patients with type 2 diabetes.

In July 2007 a meta-analysis of the FDA showed (again) that combination therapy of rosiglitazone increased the risk of congestive heart failure and myocardial ischemia [11]. Subsequently, the FDA concluded that co-administration of rosiglitazone and insulin should not be recommended and a warning was added to the label of rosiglitazone in the US [12].

In contrast, the EMA decided at the end of 2007 to remove the contraindication against use of rosiglitazone in combination with insulin [13].

Although due to these decisions the labelling of rosiglitazone became similar in the US and the EU, it is remarkable that the FDA tried to restrict the use of rosiglitazone in combination with insulin, while at the same time the EMA made a decision that would presumably increase the use of rosiglitazone in combination with insulin.

4. Requested phase IV trials

At the time of approval the applicant was recommended by the EMA to undertake an adequate post-marketing clinical trial with cardiovascular safety as primary endpoint to address the concerns about the cardiovascular safety. GSK committed to perform a long-term cardiovascular morbidity/mortality study in patients treated with rosiglitazone in combination with sulphonylurea or metformin (RECORD trial) [1].

After the results of the trial were published, the design of the trial was criticised by the scientific community, members of the FDA and even members of the EMA [1, 3, 14–16].

According to Thomas Marciniak, a member of the FDA's Division of Cardiovascular and Renal Drug Products (DCRP), the protocol of the RECORD trial would have been judged unacceptable if it was reviewed by the FDA prior to study implementation [3].

It took the FDA itself approximately 8 years to make the decision that a study, specifically designed to address the cardiovascular safety of rosiglitazone (TIDE), was needed [17].

5. Review of marketing authorisation in 2007/2008

In May 2007 the meta-analysis of Nissen et al. was published [18]. They concluded that rosiglitazone was associated with a statistically significant increased risk of myocardial infarction [18]. Subsequently, the FDA and EMA started reviewing the market authorisation of rosiglitazone based on the available data. Findings of meta-analyses performed by the FDA and GSK were consistent with the meta-analysis of Nissen et al. [2, 11].

An interim analysis of the RECORD trial showed no difference in cardiovascular deaths between rosiglitazone and metformin or sulphonylurea and a statistically non-significant rise in myocardial infarction [19]. As also described by others, this study had several limitations that decreased the validity of its results.

The available studies at that time increased the concerns regarding the cardiovascular safety, particularly regarding myocardial infarction, of rosiglitazone.

Although there was a signal of a serious adverse drug reaction, none of the studies [11, 18–24] could be considered as conclusive [25].

The EMA concluded in October 2007 that the data on the risk for ischemic heart disease was inconsistent and considered that rosiglitazone still had a place in the treatment of patients with type 2 diabetes after careful individual benefit risk assessment [26].

In July 2007 the FDA held a joint public meeting of the Endocrinologic and Metabolic Drugs and Drug Safety and Risk Management Advisory Committees. Following this advisory committee meeting there was an important discrepancy in opinions within the FDA regarding the appropriate regulatory actions. The Office of New Drugs (OND) concluded that there was not sufficient evidence to support market withdrawal and they recommended strengthening of the labelling for cardiovascular risk. They also decided that a prospective cardiovascular outcomes trial should be conducted [27].

In contrast with this, the Office of Surveillance and Epidemiology (OSE, formerly the Office of Drug Safety) argued in October 2007 that rosiglitazone should be removed from the market. They argued that, although the available data did not provide definitive proof of a risk of myocardial ischemia, the seriousness of the risk and its public health implications outweighed the uncertainty about the risk [28].

Dr. Woodcock, director of the Center for Drug Evaluation and Research of the FDA, concluded that rosiglitazone should not be withdrawn from the market in the US, provided that labelling would be changed. Consequently in November 2007, a boxed warning was added to the US label of rosiglitazone [17].

6. Review of marketing authorisation in 2010 by the FDA

After the review of 2007, new important data became available. The final results of the RECORD trial [29], an observational study of Graham et al. that compared rosiglitazone with pioglitazone [30] and also an updated meta-analysis of Nissen et al. were published [31]. Following these publications, the EMA and FDA both started reviewing the market authorisation of rosiglitazone again.

Given the intensive debate about rosiglitazone, the FDA published the grounds for their decision in the *New England Journal of Medicine* [5].

As Dr. Woodcock already stated based on the available data, in 2010 it even seemed less likely than in 2007 that rosiglitazone increases cardiovascular or all-cause death compared to non-TZD antidiabetic drugs [32]. Moreover, there does not seem to be less uncertainty about the cardiovascular safety of rosiglitazone compared to non-TZD antidiabetic agents in 2010 compared to 2007.

A number of epidemiologic studies did compare cardiovascular outcomes and/or mortality in patients using either rosiglitazone or pioglitazone [30, 32–43].

Based on the results of these observational studies it seems reasonable to prefer the use of pioglitazone, in the absence of controlled trial data. A minority of the voting panel (7 of 33 members) at the FDA advisory committee meeting of July 14, 2010, felt that these data were sufficient to raise a significant safety concern about an increased risk of mortality with rosiglitazone compared to pioglitazone [28]. In contrast, the majority of the voting panel (21 of 33 members), felt that the available data were sufficient to raise a significant concern about an increased risk of ischemic heart disease with rosiglitazone compared to pioglitazone [28].

Since the epidemiologic data were less consistent regarding the risk of ischemic heart disease than for the risk of all-cause death, the advisory committee probably did not place much weight on the observational studies.

Therefore, the opinion of the majority of the voting panel seems to be primarily based on the results of the comparison of the meta-analyses of rosiglitazone and pioglitazone. A major limitation of cross-comparison of the meta-analyses is that the patients in the control groups and the add-on therapy differed between both meta-analyses [44]. Consequently, the results of this comparison should be interpreted with caution.

In summary, compared to 2007 there seems to be no important changes regarding the uncertainty about the cardiovascular safety of rosiglitazone. This is also reflected by the fact that the OSE and OND did not change their views compared to 2007 [17, 28].

It seems that the difference in the regulatory actions between 2007 and 2010 reflects the unease to make a decision based on inconclusive data. While in 2007 the FDA and EMA could postpone a more radical decision because the final results of the RECORD trial were not available, in 2010 this was not an option anymore, since the final results of the RECORD trial were available and no results were expected of the TIDE study, since this trial had been put on hold in July 2010.

7. Suspension of marketing authorisations by the EMA

While the EMA concluded in March 2010 that the marketing authorisation of rosiglitazone should be renewed, a half year later the EMA decided that rosiglitazone should be withdrawn from the European market. Important data became available after March 2010 [30, 31, 44, 45].

The EMA considered that the meta-analyses of Nissen et al. [31] and the FDA [44] confirmed and provided additional weight to the previous analyses and the similar results presented by GSK and the FDA in their meta-analyses [7].

Based on the updated meta-analyses, compared to 2007, it seems less likely that rosiglitazone increases the risk of cardiovascular death compared to non-TZD antidiabetic agents [32]. Furthermore, the updated meta-analyses have generally still the same limitations. Most trials included in the updated meta-analyses were short-term and not designed to address the cardiovascular safety of rosiglitazone and lacked adjudication of cardiovascular events [31, 44].

The EMA considered that the cross-comparison of the pioglitazone and rosiglitazone meta-analyses of the FDA contributed to the analysis of the cardiovascular risk of rosiglitazone and to its overall benefit-risk assessment [7].

Despite its limitations, the study that assessed the proportion of patients with cardiac failure or history of cardiac failure and acute coronary syndrome (both contraindications) treated with rosiglitazone may have contributed substantially to the decision of the EMA. The results suggested that the effectiveness of the implemented risk minimisation measures was limited [7, 46]. Because no further realistic effective risk minimisation measure could be identified, the EMA suspended the marketing authorisation of rosiglitazone [7].

According to the FDA Commissioner, Dr. Hamburg, the EMA had reached similar conclusions about the safety of rosiglitazone. The different actions taken by the EMA and FDA reflected the difference between regulatory powers available in the EU and the US [47]. However, the FDA decision implies that the health benefits of rosiglitazone exceed its risk for patients who will receive rosiglitazone under the REMS system, while the EMA concluded that no such group of patients could be identified.

8. What should we learn?

The rosiglitazone story underscores the need for a robust evidence base to demonstrate the cardiovascular safety of antidiabetic drugs and the safety of drugs in general. Consequently, the FDA (in 2008) and EMA (in 2010) both proposed draft guidance for data requirements concerning the knowledge of the safety profile of new antidiabetic drugs [48–50]. The guidelines of the FDA require predefined upper boundaries of 95% confidence intervals of risk ratios, which are 1.8 for pre-marketing and 1.3 for

post-marketing studies. It should be noted that the risk ratios estimated by the meta-analysis of rosiglitazone are above these values.

In 2007, the FDA and EMA started reviewing the market authorization of rosiglitazone following the meta-analysis of Nissen et al. [18]. This meta-analysis could only be performed after the manufacturer had to put all its recent clinical studies on a website [3].

Without access to the trial reports this meta-analysis would not have been possible and rosiglitazone could have been longer or still be on the market without significant discussion. This underlines the critical importance of publicly available trial results data.

Silvio Garattini suggested that drug approval should be separated from post-marketing pharmacovigilance [51]. The effect of such a measure can be illustrated by the FDA situation, where the OSE recommended withdrawal of rosiglitazone, while the OND recommended continued marketing of rosiglitazone. This suggests that if a safety evaluation board like the OSE had the authority to decide whether drugs should be withdrawn from the market, rosiglitazone would have been withdrawn from the market in 2007.

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