doi: 10.1111/fcp.12207

ORIGINAL ARTICLE

Impact of rosiglitazone safety alerts on oral antidiabetic sales trends: a countrywide study in Portugal

Maria T. Herdeiro[a,b]*, Sara Soares[a], Tânia Silva[c], Fátima Roque[a,d], Adolfo Figueiras[e]

[a]*Department of Medical Sciences and Institute for Biomedicine – iBiMED, University of Aveiro, Campus Universitário de Santiago, 3810-193, Aveiro, Portugal*
[b]*CESPU, Instituto de Investigação e Formação Avançada em Ciências e Tecnologias da Saúde, Rua Central de Gandra, 1317 4585-116, Gandra, Portugal*
[c]*IMS Health Portugal, Lagoas Park Edifício 3-piso, 32740-266, Oeiras, Portugal*
[d]*Research Unit for Inland Development, Polytechnic Institute of Guarda (UDI/IPG), Av. Dr. Francisco Sá Carneiro n°50, 6300-559, Guarda, Portugal*
[e]*Consortium for Biomedical Research in Epidemiology & Public Health (CIBER en Epidemiología y Salud Pública-CIBERESP), University of Santiago de Compostela, R/ de San Francisco, s/n15782, Santiago de Compostela, Spain*

Keywords
oral antidiabetic drugs,
rosiglitazone,
safety alerts,
sale trends

Received 7 February 2016;
revised 12 May 2016;
accepted 2 June 2016

*Correspondence and reprints:
teresaherdeiro@ua.pt

ABSTRACT

Pharmacovigilance systems are important to monitor the safety of on-market drugs after approval. The aim of this study was to assess the impact of rosiglitazone safety alerts on trends in the sale of rosiglitazone and other oral antidiabetic drugs. An ecological study was conducted, using temporally aggregated data and linking safety alerts to countrywide sales of all oral antidiabetic drugs in Portugal from January 2002 to December 2012. Sales figures for oral antidiabetic drugs marketed in Portugal were supplied by IMS Health Portugal with a breakdown by active substance and fixed combinations. The number of defined daily doses per 1000 inhabitants per day (DIDs) of each oral antidiabetic drug sold to the estimated diabetic population using oral antidiabetic drugs in Portugal was calculated. Particular attention was paid to the case of rosiglitazone, with the results being adjusted for changes in rosiglitazone reimbursement policies. A total of four safety alerts were issued about rosiglitazone. Rosiglitazone sales registered an increase of 32.9% (0.202 DIDs; $P < 0.001$) after the first alert (risk of macular oedema or worsening of pre-existent macular oedema) in January 2006. After subsequent alerts about cardiovascular risks, this trend was not, however, repeated and sales fell. Following the January 2006 and January 2008 safety alerts, rosiglitazone sales described a long-term downward trend, with decreases of 3.75% (−0023 DIDs; $P > 0.05$) and 0.24% (−0.001 DIDs; $P > 0.05$), respectively. It is important to promote the dissemination and publication of drug safety alerts.

INTRODUCTION

Drug safety information at the time a new drug is placed on the market is limited; consequently, drug authorities have developed and implemented pharmacovigilance systems that monitor the safety of on-market drugs after approval [1]. If a signal is detected, there is a benefit–risk evaluation, which can affect decision-making in different ways, ranging from direct communication to health professionals in the form of a 'Dear Doctor' letter, restriction to approved indications, new contraindications, new or reinforced warnings, urgent safety restrictions, or even suspension or withdrawal of marketing authorization [2,3].

Rosiglitazone is an oral antihyperglycaemic agent, from the group of thiazolidinediones, used to maintain glucose homoeostasis and control type 2 diabetes, and is one example of the importance of the role of pharmacovigilance. According to the Portuguese Guidelines of the Directorate-General of Health, thiazolidinediones are important to the management of diabetes type 2 in double therapy when patients show marked resistance to insulin [4].

The drug was first authorized in Portugal in July 2000, and several safety alerts have been published [5–7] following its market suspension in November 2010 [6,8–10].

Previous studies have assessed the impact of safety alerts on drug prescribing, dispensing and sales [11–18], with inconsistent results [19,20]. In the case of rosiglitazone, the safety alerts also had an uneven impact on drug sales in different settings [13–17], and there are authors who report a delay in the effect of such alerts.

Accordingly, this study sought to evaluate the impact of these measures in Portugal by: (i) analysing the impact of rosiglitazone safety alerts on sales trends for rosiglitazone and other oral antidiabetic drugs (OAD); and (ii) comparing the impact of different types of rosiglitazone safety alerts according to the nature of the alert (ocular or cardiovascular risk).

MATERIALS AND METHODS

Settings

The study covered almost the entire Portuguese population, using data on total sales of oral antidiabetic drugs (not including insulin). Prevalence of diagnosed diabetes in Portugal is 7.2%, with 90% of those affected having type 2 diabetes and thus being potential users of oral antidiabetic drugs [21].

The Portuguese National Health Service is universal, general and largely free of charge. Moderate fees are applied according to each person's individual situation, for example with exemptions for pregnant women, children aged under 12 years, economically inactive persons, blood donors, alcoholics and drug dependents while in recovery programmes, and patients with chronic diseases such as diabetes [22]. Reimbursement policies vary according to patients' financial and clinical situation [23,24].

Rosiglitazone was first authorized on 11 July 2000, and four alerts were issued over the course of its lifespan, namely in January 2006, May 2007, January 2008 and September 2010. In November 2010, the drug was suspended. The first alert – alert a) in January 2006 – voiced safety concerns about rosiglitazone-related development of macular oedema or worsening of pre-existing macular oedema. The second alert – alert b) in May 2007 – was issued after the publication of a meta-analysis that associated rosiglitazone use with increased risk of myocardial infarction and risk of death. The third alert – alert c) in January 2008 – recommended that the patient leaflet and summary of the product's characteristics be updated; and lastly, the fourth alert – alert d) in September 2010 – recommended the market suspension of the drug due to its association with increased risk of cardiovascular complications. Reimbursement policies also changed during the time that rosiglitazone was on the market, with the rate rising from 20% during the period July 2003–December 2006 (the rate for other OAD was 95%) to 95% in January 2007 (being equal to other OAD).

Design

The study had an ecological design, using temporally aggregated (monthly) data on the sales of all oral antidiabetic drugs in Portugal across the period January 2002–December 2012. Although the impact of safety alerts on rosiglitazone has been described in the USA [12,16,17,25] and Europe [13,15,18], relatively little is known about rosiglitazone sales trends in Portugal following safety alerts. The study was conducted after the market withdrawal of rosiglitazone, thus not influencing sales in any way.

Variables and data sources

A search was made in the National Portuguese Authority for Medicines & Health Products (*Autoridade Nacional do Medicamento e Produtos de Saúde I.P. – INFARMED*) website [26], which is updated daily, and the Pharmacovigilance Bulletin (PhB) [27] published quarterly by INFARMED. The data retrieved were supplemented with information posted on the European Medicines Agency (EMA) website [10]. Selection was based on the type of alert, specifically targeting those relating to drug safety.

Data on the sale of oral antidiabetic drugs (not including insulin) by distributors to pharmacies were supplied by IMS Health Portugal. Active substances were classified according to the WHO Anatomical Therapeutic Chemical Index 2013 and were used to obtain the defined daily dose (DDD) per 1000

inhabitants per day (DID) for each pharmaceutical presentation [11,14,28].

A breakdown of sales trends of all oral antidiabetic drugs marketed in Portugal was obtained by active substance and fixed combination. We then calculated DDDs per presentation of active substance per month and the number of DIDs sold (DDDs per thousand inhabitants per day by the estimated diabetic population using oral antidiabetic drugs in Portugal) for each oral antidiabetic drug [20,28]. Results were adjusted both for changes in the rosiglitazone reimbursement rate (from 20%, [29] to 95%, [30]) and, due to Portuguese Government budgetary constraints, for the change in the reimbursement rate for all oral antidiabetic drugs to 90% in October 2010 [23,24].

Statistical analysis

A segmented regression analysis model [31] was designed to analyse the differences observed after each of the four rosiglitazone safety alerts. Values were deemed significant in any case where $P < 0.05$. The 95% confidence interval (95% Confidence Interval) for the coefficients (postalert changes in DIDs in the short term and long term, and associated with a unit of time, i.e. month) [32] afforded 95% assurance of nonrandom information per alert. The dependent variable was defined as the DID per active substance (rosiglitazone and pioglitazone), group (thiazolidinediones, i.e. rosiglitazone and pioglitazone; sulphonylureas; biguanides, gliptins, intestinal alpha-glucosidase inhibitors and meglitinides) and fixed combination (metformin–rosiglitazone; metformin–pioglitazone; metformin–vildagliptin; metformin–sitagliptin; glibenclamide–metformin; and glimepiride–pioglitazone). The independent variables were defined as: time (t : 1, 2, 3...), a binary variable taking values of 0 before and 1 after the safety alert, and used to see the immediate leap in sales caused by a given safety alert (short term); and a variable for the time elapsed since the alert, which took the value of 0 before and values of 1, 2, 3... after each alert, and used to see the gradual change after a given safety alert (long term). These two variables, defined by short and long periods after safety alerts, were, respectively, level, that is the value at the beginning of a given time interval, showing the immediate value following each change point as a jump or drop after the safety alert, and trend, that is a given measure's rate of change, showing the gradual shift over time after each safety alert [31].

Values were adjusted for changes in rosiglitazone reimbursement policies (20%, [29] 95% [30]), using a binary variable with values of 0 before and 1 after changes in the reimbursement policy.

The percentage change in sales of oral antidiabetic drugs following rosiglitazone safety alerts was calculated on the basis of the coefficients obtained through statistical analysis of postalert changes in the short and long term, and on the baseline value, calculated for the 3 months preceding each alert (January 2006, May 2007, January 2008 and September 2010).

RESULTS

Table I shows the lifespan of rosiglitazone from market authorization to suspension or withdrawal of marketing authorization, the outcomes of each safety alert (identified through the INFARMED and EMA websites and the INFARMED Pharmacovigilance Bulletin), and changes in Portuguese reimbursement policies for this drug.

Figure 1 depicts the sales trends for rosiglitazone and pioglitazone, by reference to total oral antidiabetic drugs sold. Rosiglitazone sales showed a statistically significant short-term increase of 32.9% (0.202 DIDs; $P < 0.001$) after the first alert (alert a).

In 2007, following a rise in the reimbursement rate (r), a sudden increase from 20% to 95%, there was a new increase in rosiglitazone sales. Subsequently, sales started to decline, registering an initial short-term decrease of 7.6% (−0.041 DIDs; $P > 0.05$) after the second alert (alert b) and an even greater short-term decrease of 42.87% (−0.183 DIDs; $P < 0.05$) after the third alert, until the drug's market suspension following the fourth alert (alert d).

Figure 1 also shows that pioglitazone sales registered an increase in January 2010. With respect to long-term trends, after safety alerts a) and c) rosiglitazone sales fell by 3.75% (−0023 DIDs; $P > 0.05$) and 0.24% (−0.001 DIDs; $P > 0.05$), respectively.

This can be seen in *Table* II, which shows the differences in drug sales for the various groups of oral antidiabetic drugs in the short term immediately following each of the four rosiglitazone safety alerts and their effect over the longer term. In the short term, postalert effects were seen as immediate changes in the DID, and in the long term as changes in the DID associated with a unit of time (month).

Pioglitazone displayed a negative short-term trend after each rosiglitazone alert, which reached statistical significance after alert c) with a decrease of 0.004 ($P = 0.003$).

Table I Rosiglitazone lifespan.

Data	Communications	Outcomes	Alterations	Agency
11-July-2000	Rosiglitazone – Market authorization	Rosiglitazone Market Authorization for drugs containing rosiglitazone in the European Union	Not applicable	EMA
03-July-2003	Rosiglitazone – Reimbursement	Rosiglitazone reimbursement rate of 20% vs. 100% for other oral antidiabetic drugs	Not applicable	INFARMED
Jan-2006	Rosiglitazone – Macular oedema risk – alert a)	Rosiglitazone safety concerns: macular oedema or worsening of pre-existing macular oedema	Evaluation by European Regulatory Authorities	INFARMED Pharmacovigilance Bulletin
01-Jan-2007	Rosiglitazone – Reimbursement	Rosiglitazone reimbursement rate of 95%	Rosiglitazone reimbursement rate increased from 20% to 95%	INFARMED
21-May-2007	Rosiglitazone – Publication of meta-analysis (online) in the New England Journal of Medicine [7]	Rosiglitazone: association with increase in risk of myocardial infarction and risk of death from cardiovascular causes	Not applicable	Not applicable
22-May-2007	Rosiglitazone	Safety alert published by the FDA Process evaluation by CHMP	Not applicable	EMA INFARMED
23-May-2007	Rosiglitazone – Information on cardiac safety – alert b)	Rosiglitazone safety concerns: cardiac effects	Not applicable	EMA INFARMED
14-June-2007	Rosiglitazone – Publication of meta-analysis (in press) in the New England Journal of Medicine [7]	Rosiglitazone: association with increase in risk of myocardial infarction and risk of death from cardiovascular causes	Not applicable	Not applicable
18-Oct-2007	Rosiglitazone and Pioglitazone – EMA states that the benefit–risk profile is positive	Rosiglitazone safety concerns: cardiac effects	Rosiglitazone prescriptions should be updated and should include warnings about ischaemic heart disease patients, and rosiglitazone should only be used in association with insulin under extreme surveillance	EMA INFARMED
24-Jan-2008	Rosiglitazone – Recommendation of new warnings and contraindications – alert c)	Update of SPC and PL	New warning to the effect that rosiglitazone should not be used in patients with ischaemic heart disease and/or peripheral arterial disease; and a new contraindication that it should not be used in patients with acute coronary syndrome	EMA INFARMED
28-June-2010	Rosiglitazone – Publication of an updated meta-analysis (online) in Archives of Internal Medicine (34)	Rosiglitazone: increase in risk of myocardial infarction	Not applicable	Not applicable
09-Jul-2010	Rosiglitazone – Beginning of benefit–risk assessment	Rosiglitazone: review of information to assess new data effect on the benefit–risk profile	Not applicable	EMA INFARMED
22-Jul-2010	Rosiglitazone – Further review of benefit–risk assessment	Revision and evaluation of benefit–risk data on rosiglitazone drugs	Not applicable	EMA INFARMED
26-Jul-2010	Rosiglitazone – Publication of an updated meta-analysis (in press) in Archives of Internal Medicine [33]	Rosiglitazone: increase in risk of myocardial infarction	Not applicable	Not applicable

Table I. Continued

Data	Communications	Outcomes	Alterations	Agency
23-Sep-2010	Rosiglitazone – Recommendation of market suspension – alert d)	Rosiglitazone: association with increased cardiovascular risk	Recommendation of market suspension	EMA INFARMED
29-Sep-2010	Rosiglitazone – Communication to health professionals about suspension of market authorization in the European Union (validated in September 2010)	Recommendation of market suspension	'Dear doctor letter'	GlaxoSmithKline – Produtos Farmacêuticos Lda EMA INFARMED
10-Nov-2010	Rosiglitazone – Market suspension	Recommendation of market suspension	GlaxoSmithKline – Produtos Farmacêuticos Lda. proceeds with voluntary collection of all drug batches containing rosiglitazone INFARMED orders immediate suspension of the marketing and sale of these products	EMA INFARMED

FDA, Food and Drug Administration; EMA, European Medicines Agency; CHMP, Committee for Medicinal Products for Human Use; SPC, Summary of Product Characteristics; PL, patient leaflet; INFARMED, National Authority of Medicines and Health Products, IP.
Safety alerts used to study drug trends are marked in grey [5–7,10,29–31].

Combinations of rosiglitazone with other drugs registered downward sales trends in the short term after each alert. After alert d), which led to the suspension of rosiglitazone, the fixed combination of glimepiride–pioglitazone showed a statistically significant rising trend in both the short (151.0%) and long term (3.6%), with values of 0.001 ($P < 0.001$) and 2.383×10^{-5} ($P < 0.001$), respectively. Metformin–pioglitazone likewise displayed an upward trend soon after alert c). The other alerts were followed by a downward trend in sales in both the short and long term.

After the last rosiglitazone safety alert, a number of groups registered statistically significant rising trends in the short and long term, namely sulphonylureas [3723.0% (11.655 DIDs; $P = 0.001$) in the short term and 421.0% (1.318 DIDs; $P < 0.001$) in the long term]; intestinal alpha-glucosidase inhibitors [2656.0% (0.611 DIDs; $P = 0.001$) in the short term and 795.0% (0.183 DIDs; $P < 0.001$) in the long term]; and the fixed combination of glibenclamide–metformin [5915.0% (0.394 DIDs; $P = 0.005$) in the short term and 660.0% (0.044 DIDs; $P = 0.001$) in the long term].

In contrast, other drugs, such as biguanides and the fixed combinations of metformin–vildagliptin and metformin–sitagliptin, displayed an opposite tendency after the last rosiglitazone safety alert. These active substances described statistically significant decreasing trends, with short-term postalert values of 19.0% (18.100 DIDs; $P = 0.001$), 18.2% (9.348 DIDs; $P = 0.020$) and 48.4% (17.294 DIDs; $P < 0.001$), and long-term postalert values of 2.44% (2.301 DIDs; $P < 0.001$), 3.1% (1.581 DIDs, $P < 0.001$) and 3.9% (1.691 DIDs; $P < 0.001$), respectively.

DISCUSSION

Whereas rosiglitazone sales decreased after the safety alerts which voiced cardiovascular concerns, there was no such decrease after the safety alert that indicated risk of macular oedema or worsening of pre-existing macular oedema. On evaluating the impact of rosiglitazone safety alerts, our results show that: (i) the overall rosiglitazone sales trend was downward; (ii) drug sales of fixed combinations using rosiglitazone, such as metformin–rosiglitazone, also decreased across the study period; and (iii) rosiglitazone was replaced, not by drugs from the same pharmacotherapeutic group, but instead by sulphonylureas (which registered a significant increase in sales after the last rosiglitazone safety alert) [17].

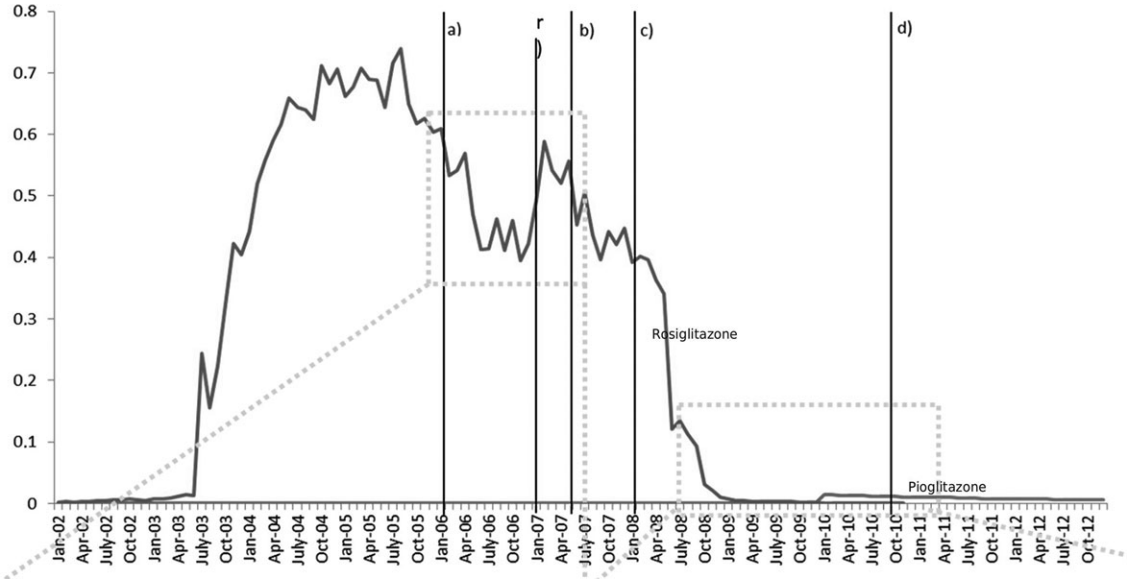

Figure 1 Sales of rosiglitazone and pioglitazone (DIDs) by reference to the total of oral antidiabetic drugs sold. a) European Regulatory Authorities issue safety alert about the use of rosiglitazone and macular oedema or the worsening of pre-existing macular oedema (January 2006). b) European Medicines Agency (EMA) issues safety alert about the cardiac effects of rosiglitazone (May 2007). c) EMA recommends new warnings and contraindications (January 2008). d) EMA recommends market suspension (September 2010). r) Change in the rosiglitazone reimbursement policy (from 20% to 95%). DID, defined daily dose/1000 inhabitants/day.

As is well known, there are undesirable side effects associated with the use of drugs, and rosiglitazone is no exception [7,12–17,19,25,34,35]. Furthermore, diabetes prevalence levels are high [21] and so oral antidiabetic drugs are used by a large number of persons worldwide. It is thus important to assess the impact of safety alerts on drug sales patterns, in order to assess the efficacy and efficiency of communication channels in the dissemination of these alerts to health professionals and patients alike. Rosiglitazone assumes greater importance due to the cardiovascular effects associated with its use.

Bearing in mind the adverse events associated with rosiglitazone use and in line with the literature [13,14,16,25], our results show that safety alerts published by the EMA [36] and INFARMED [5] have an impact on drug sales.

Assessment of the overall sales trends for rosiglitazone in Portugal showed that safety alerts influenced this oral antidiabetic drug's market lifespan, a finding in line with those reported by other studies undertaken in the United States [12,16,17,25] and Europe [13,15,18]. Moreover, the effects of such safety alerts are immediately felt on drug sales. While these results are consistent with those of Stewart et al. (2009) [17], they nevertheless differ from some studies which found that a downward trend in prescriptions only became observable after several safety alerts [14], and others which reported that an upward trend in sales was maintained after alerts, albeit at a lower rate [37].

Comparison of the magnitude of the effect of the three safety alerts issued in Portugal from 2005 to 2008 indicated a 98.4% decrease in rosiglitazone sales; and when Ruitter et al. [13] (June 2012) analysed differences in prescribing trends among general practitioners and specialists in the Netherlands over the self-same period, they observed that the EMA press releases were followed by an overall downward trend. Similarly, Starner et al. [16] (July–August 2008) reported a 48.8% decrease in the number of rosiglitazone users across the period January 2007–May 2008, a time when there were two safety alerts in Portugal accompanied by a 31.02% decrease in rosiglitazone sales. Cohen et al. [25] (April 2010) likewise observed a 60% decline in rosiglitazone use following FDA warnings between February 2007 and May 2008, a period during which two safety alerts were issued in Portugal with an ensuing 42.2% fall in rosiglitazone sales. Lastly, the study conducted by Shah et al. [12] (November 2010) revealed a 75.6% drop in the

Table II Differences in short- and long-term postalert drug trends.

		Alert a)		Alert b)		Alert c)		Alert d)	
	Period	Coefficient	95% CI	Coefficient	95% CI	Coefficient	95% CI	Coefficient	95% CI
Rosiglitazone	Short	0.202**	−0.305/−0.99	−0.041	−0.174/0.093	−0.183*	−0.291/−0.075	0.084*	0.008/0.161
	Long	−0.023	−0.037/−0.010	0.004	−0.022/0.030	−0.001	−0.024/0.022	0.010**	0.005/0.014
Pioglitazone	Short	-1.6×10^{-16}	−0.003/0.003	-9×10^{-16}	−0.004/0.004	−0.004*	−0.007/−0.001	0.000	−0.002/0.002
	Long	1.5×10^{-17}	0.000/0.000	1.7×10^{-16}	−0.001/0.001	0.000*	0.000/0.001	−0.001**	−0.001/−0.001
Thiazolidinediones	Short	−0.202**	−0.305/0.098	−0.041	−0.175/0.094	−0.188*	−0.0296/−0.079	0.084*	0.007/0.161
(Rosiglitazone + Pioglitazone)	Long	−0.023*	−0.037/−0.009	0.004	−0.023/0.030	0.001	−0.023/0.022	0.009**	0.004/0.014
Sulphonylureas	Short	0.814	−8.170/9.799	0.568	−12.228/11.091	−23.512**	−32.924/−14.100	11.655*	4.974/18.337
	Long	0.086	−1.098/1.270	−0.312	−2.592/1.968	−1.073	−3.051/0.904	1.318**	0.921/1.716
Biguanides	Short	−0.988	−13.668/11.691	1.042	−2.915/3.521	−3.749	−17.032/9.534	−18.100*	−27.529/−8.670
	Long	−0.053	−1.724/1.618	0.303	−15.412/17.497	2.100	−2.862/−1.740	−2.301**	−0.254/0.406
Gliptins	Short	2.260×10^{-15}	−0.010/0.010	-2.509×10^{-15}	−0.013/0.013	−0.015*	−0.026/0.005	−0.006	−0.013/0.002
	Long	-3.9×10^{-13}	−0.001/0.001	1.055×10^{-15}	−0.003/0.003	0.002	0.000/0.004	−0.002**	−0.003/−0.002
Intestinal alpha-glucosidase	Short	0.376	−0.898/1.649	−4.34	−0.318/0.329	−3.078**	−4.413/−1.744	1.611*	0.664/2.559
inhibitors	Long	−0.010	−0.178/0.158	0.006	−2.087/1.220	−0.115	−0.395/0.166	0.183**	0.127/0.239
Meglitinides	Short	2.156×10^{-16}	−0.001/0.001	-4.416×10^{-17}	−0.002/0.002	−0.002	−0.004/−0.001	−0.002	−0.002/0.000
	Long	-4.735×10^{-17}	0.000/0.000	7.044×10^{-17}	0.000/0.000	0.000	0.000/0.001	0.000**	0.000/0.000
Glibenclamide–Metformin	Short	−0.089	−0.455/0.277	0.012	−0.463/0.487	−0.779**	−1.163/−0.395	0.394*	−0.122/0.666
	Long	−0.049*	−0.097/0.000	−0.009	−0.102/0.084	−0.050	−0.131/0.030	0.044**	0.028/0.061
Glimepiride–Pioglitazone	Short	-2.036×10^{-17}	0.000/0.000	-6.044×10^{-17}	0.000/0.000	0.000	0.000/0.000	0.001**	0.001−0.001
	Long	2.790×10^{-18}	0.000/0.000	1.024×10^{-27}	0.000/0.000	1.047×10^{-5}	0.000/0.000	2.383E−5**	0.000/0.000
Metformin–Rosiglitazone	Short	2.336×10^{-15}	−0.010/0.010	-2.202×10^{-15}	−0.013/0.013	−0.014**	−0.024/0.004	−0.036**	−0.044/−0.029
	Long	-4.511×10^{-16}	−0.001/0.001	1.055×10^{-15}	−0.003/0.003	0.002	−0.001/0.004	−0.002**	−0.002/−0.001
Metformin–Pioglitazone	Short	-5.197×10^{-13}	−13.671/13.671	-5.897×10^{-13}	−17.741/17.741	30.558	16.236/44.880	4.792	0.190/1.400
	Long	1.448×10^{-13}	−1.802/1.802	-1.197×10^{-13}	−3.469/3.469	−0.915	−3.924/2.094	0.795*	−5.374/14.959
Metformin–Vildagliptin	Short	2.136×10^{-13}	−10.548/10.548	-4.169×10^{-12}	−13.688/13.688	9.184	−1.866/20.234	−9.348	−17.192/−1.504
	Long	-4.073×10^{-13}	−1.390/1.390	1.378×10^{-12}	−2.677/2.677	1.637	−0.685/3.958	−1.581	−2.048/−1.115
Metformin–Sitagliptin	Short	-2.847×10^{-14}	−9.532/9.532	-5.299×10^{-12}	−12.370/12.370	2.140	−7.846/12.126	−17.294**	−24.383/−10.205
	Long	2.883×10^{-15}	−1.256/1.256	9.872×10^{-13}	−2.419/2.419	1.762	−0.336/3.860	−1.691**	−2.113/−1.269

CI, confidence interval.

Coefficient: postalert changes in DIDs in the short term and long term, and associated with a unit of time (month).

$^{**}P < 0.001$; $^{*}P < 0.05$.

number of monthly rosiglitazone prescriptions (going from 1.3 million in January 2007 to almost 317 000 in June 2009) linked to the publication of one alert in May 2007. During the same period, there were two rosiglitazone safety alerts in Portugal, one in May 2007 and another in January 2008, and here too there was a sharp fall in rosiglitazone sales (a 99.3% reduction in DIDs sold).

Oral antidiabetic drugs were seen to behave differently according to whether a safety alert was non-life-threatening or life-threatening. Our results are consistent with those obtained elsewhere, which report that non-life-threatening safety alerts either had no effect [20,38,39] or that the effect was felt only after several such alerts [14].

After alert a) for ocular problems associated with rosiglitazone use (non-life-threatening), there was a change in the reimbursement policies for this drug, leading to a reduced cost to the patient. Indeed, it is this very aspect that might have influenced rosiglitazone sales, which actually rose after alert a), contrary to what might have been expected. Changes in reimbursement policies might thus have an influence on drug sales, with lower costs leading to increased sales.

Analysis of the overall sale trends showed that, contrary to what might have been expected [17,25], sales of pioglitazone did not directly increase in response to the decrease in rosiglitazone sales. This might be explained by the fact that, after the alerts, not all prescribers chose to replace rosiglitazone with the thiazolidinedione group: some chose other groups, such as sulphonylureas, intestinal alpha-glucosidase inhibitors or glibenclamide–metformin in a fixed combination [15,17]. Fixed combinations containing rosiglitazone and pioglitazone displayed a tendency to decrease across the study period, except after alert c), when a short-term increase was observed in metformin–pioglitazone, something that might be accounted for by official approval of marketing authorization in December 2007.

There was a wide variation in the rates of change registered by the different pharmacotherapeutic groups, for example following the last rosiglitazone safety alert, the long-term change in sulphonylurea sales was 421.0% versus 2.4% for biguanides. This might be explained by the fact that the baseline value of sulphonylurea sales (0.313 DIDs for the 3 months leading up to the safety alert) was smaller than the baseline value of biguanide sales (94.2 DIDs). This would mean that smaller baseline values were accompanied by greater percentage changes.

This was a countrywide study, and the authors are unaware of any other study of this type conducted in Portugal. The study uses data on oral antidiabetic drug sales to pharmacies in Portugal (thereby giving a close approximation of real use by the overall population using this type of medication from January 2002 to December 2012) to assess trends in drug sales before and after rosiglitazone safety alerts [17,40]. The data analysed pertained to rosiglitazone and other oral antidiabetic drugs, thus enabling drugs used as a post-alert alternative to rosiglitazone to be studied.

An important limitation of our study is the impossibility of measure some possible interfering factors like the effect on sales change of new OAD on market between the study period and the influence of changes on sociodemographic characteristics of the patients as a result from the changes in the economic situation of the country. Other limitation is that the data we used are sales data, not prescription data, so we cannot analyse the sales of rosiglitazone alone and the sales of rosiglitazone with other OAD.

As with any ecological study, other limitation of ours is the fact that the results cannot be extrapolated at an individual level. A further limitation is that the applicability of our results to other settings is not known.

One strength was, as previously recommended [40], the use of an interrupted time series for analysis purposes, with the inclusion of known external factors, like changes in reimbursement policies, as potential confounders. On the other hand, other potential confounders, such as corporate lobbying, could not be controlled for, and these could have influenced overall sales trends [17,20,40].

Our results suggest that whereas life-threatening alerts appear to have a great and almost immediate impact on drug sales and use, this would not seem to be the case with alerts which, despite not constituting a threat to life, are nonetheless important for the patient's safety. The precise reasons for these different responses on the part of health professionals would have to be studied. Even so, one of these factors is any change in reimbursement policies that tends to reduce the cost to the patient. It would therefore be advisable for health authorities not to reduce the cost to patients in any case where a drug has become the subject of a safety alert.

The main conclusion of our study is that a decreased reimbursement rate might always and quickly follow an alert and it is a very important concern for sanitary policy.

ACKNOWLEDGEMENTS

The authors would like to thank IMS Health Portugal, for making available the consumption data used in this manuscript, and to iBiMED (UID/BIM/04501/2013). Thanks must also go to Dr. Inês Vaz for her help with the revision of this manuscript.

CONFLICTS OF INTEREST

All authors declare that they have no conflict of interests.

REFERENCES

1 Ahmad S.R. Adverse drug event monitoring at the Food and Drug Administration. J. Gen. Intern. Med. (2003) **18** 57–60.
2 EMA. Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems, (2012). [cited 2013 10-02-2013]. Available from http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/09/WC500172402.pdf
3 Legislação Farmacêutica Compilada – Decreto-Lei n.° 176/2006, de 30 de Agosto, Artigo 39.° Medidas urgentes de segurança (2006).
4 DGS, Abordagem Terapêutica Farmacológica na Diabetes Mellitus Tipo 2 no Adulto [cited 09-05-2016]. Available from: https://www.dgs.pt/directrizes-da-dgs/normas-e-circulares-normativas/norma-n-0522011-de-27122011-atualizada-a-30072013.aspx)
5 INFARMED. Rosiglitazona 2013 [updated 15-02-2013; cited 2013 15-02-2013]. Available from: http://www.infarmed.pt/portal/page/portal/INFARMED/MAIS_ALERTAS/ALERTAS_DE_SEGURANCA/2007/Rosiglitazona.
6 EMA. European Medicines Agency recommends suspension of Avandia, Avandamet and Avaglim London 2013 [cited 2013 14-02-2013]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2010/09/news_detail_001119.jsp&mid=WC0b01ac058004d5c1.
7 Nissen S.E., Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N. Engl. J. Med. (2007) **356** 2457–2471.
8 INFARMED. Recomendação de suspensão: Rosiglitazona Lisboa2013 [cited 2013 14-02-2013]. Available from: http://www.infarmed.pt/portal/page/portal/INFARMED/MAIS_ALERTAS/ALERTAS_DE_SEGURANCA/Tab/Rosiglitazona%20%BF%20recomenda%E7%E3o%20de%20suspens%E3o.
9 INFARMED. Rosiglitazona – Recolha do mercado 2013 [updated 14-02-2013; cited: 14-02-2013]. Available from: http://www.infarmed.pt/portal/page/portal/INFARMED/MAIS_ALERTAS/DETALHE_ALERTA?itemid=3695292.
10 EMA. European Public Assessment Reports 2013 [cited 2013]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=%2Fpages%2Fmedicines%2Flanding%2Fepar_search.jsp&mid=WC0b01ac058001d124&searchTab=searchByKey&alreadyLoaded=true&isNewQuery=true&status=Authorised&status=Withdrawn&status=Suspended&status=Refused&keyword=rosiglitazone&keywordSearch=Submit&searchType=inn&taxonomyPath=&treeNumber=&searchGenericType=generics.
11 Nkeng L., Cloutier A.-M., Craig C., Lelorier J., Moride Y. Impact of regulatory guidances and drug regulation on risk minimization interventions in drug safety: a systematic review. Drug Saf. (2012) **35** 535–546.
12 Shah N.D., Montori V.M., Krumholz H.M., Tu K., Alexander G.C., Jackevicius C.A. Responding to an FDA warning — geographic variation in the use of rosiglitazone. N. Engl. J. Med. (2010) **363** 2081–2084.
13 Ruiter R., Visser L., Herk-Sukel M.P. et al. Prescribing of rosiglitazone and pioglitazone following safety signals. Drug Saf. (2012) **35** 471–480.
14 Wilkinson J.J., Force R.W., Cady P.S. Impact of safety warnings on drug utilization: marketplace life span of cisapride and troglitazone. Pharmacotherapy. (2004) **24** 978–986.
15 Leal I., Romio S.A., Schuemie M., Oteri A., Sturkenboom M., Trifirò G. Prescribing pattern of glucose lowering drugs in the United Kingdom in the last decade: a focus on the effects of safety warnings about rosiglitazone. Br. J. Clin. Pharmacol. (2013) **75** 861–868.
16 Starner C., Schafer J., Heaton A., Gleason P. Rosiglitazone and pioglitazone utilization from January 2007 through May 2008 associated with five risk-warning events. J. Manag. Care Pharm. (2008) **14** 523–531.
17 Stewart K.A., Natzke B.M., Williams T., Granger E., Casscells S.W., Croghan T.W. Temporal trends in anti-diabetes drug use in tricare following safety warnings in 2007 about rosiglitazone. Pharmacoepidemiol. Drug Saf. (2009) **18** 1048–1052.
18 Hall G.C., Smith H.T., Curtis B., McMahon A.D. Changes and predictors for change to thiazolidinedione prescribing in UK primary care following the rosiglitazone safety warning. Int. J. Clin. Pract. (2011) **65** 586–591.
19 Cluxton R.J., Li Z., Heaton P.C. et al. Impact of regulatory labeling for troglitazone and rosiglitazone on hepatic enzyme monitoring compliance: findings from the state of Ohio medicaid program. Pharmacoepidemiol. Drug Saf. (2005) **14** 1–9.
20 Carracedo-Martínez E., Pia-Morandeira A., Figueiras A. Impact of a health safety warning and prior authorisation on the use of piroxicam: a time-series study. Pharmacoepidemiol. Drug Saf. (2012) **21** 281–284.
21 Correia L.G., Boavida J.M., Almeida J.P.F. et al. Diabetes: Factos e Números 2012- Relatório Anual do Observatório Nacional da Diabetes. Lisboa 2013 [cited 26-02-2013]. Available from: http://www.spd.pt/images/ond2013.pdf.
22 Decreto-Lei n.° 128/2012 de 21 de junho de 2012, Republicação do Decreto-Lei n.° 113/2011, de 29 de novembro. Sect. Artigo 4° and Artigo 8° (2012).
23 Portaria n.° 924-A/2010, de 17 de Setembro, ANEXO (a que se refere o artigo 1.°) (2010).

24 Decreto-Lei n.° 106-A/2010 de 1 de Outubro Alteração ao Decreto -Lei n.° 48 -A/2010, de 13 de Maio, Artigo 5° (2010).
25 Cohen A., Rabbani A., Shah N., Alexander G.C. Changes in glitazone use among office-based physicians in the U.S., 2003–2009. Diabetes Care (2010) **33** 823–825.
26 INFARMED. Alertas Lisboa2013 [cited 2013]. Available from: http://www.infarmed.pt/portal/page/portal/INFARMED/MAIS_ALERTAS.
27 INFARMED. Boletim de Farmacovigilância Lisboa2013 [cited 2013]. Available from: http://www.infarmed.pt/portal/page/portal/INFARMED/PUBLICACOES/TEMATICOS/BOLETIM_FARMACOVIGILANCIA.
28 WHO. DDD Definition and general considerations Oslo [updated 2009-12-17; cited 2013 30-01-2013]. Available from: http://www.whocc.no/ddd/definition_and_general_considera/.
29 Mauritti M.M. A vida por um desconto. Médico de Família. (2004) **2004** 20–22.
30 Aviso n.o 1153/2007 de 24 de Janeiro de 2007, 2ª. Série (2007).
31 Wagner A.K., Soumerai S.B., Zhang F., Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. J. Clin. Pharm. Ther. (2002) **27** 299–309.
32 Field A. Discovering Statistics Using SPSS, 3rd edn, SAGE Publications Ltd, London, 2009.
33 Nissen Se W.K. Rosiglitazone revisited: an updated meta-analysis of risk for myocardial infarction and cardiovascular mortality. Arch. Intern. Med. (2010) **170** 1191–1201.
34 Dourosa A., Ebertc N., Jakobd O., Martusd P., Kreutza R., Schaeffner E. Estimating kidney function and use of oral antidiabetic drugs in elderly. Fundam. Clin. Pharmacol. (2015) **29** 321–328.
35 Dhamijaa P., Bansala D., Srinivasana A., Bhallab A., Hotaa D., Chakrabartia A. Patterns of prescription drug use and incidence of drug–drug interactions in patients reporting to medical emergency. Fundam. Clin. Pharmacol. (2013) **27** 231–237.
36 EMA. Avandia – Rosiglitazone London2013 [cited 2013 31-01-2013]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000268/human_med_000662.jsp&mid=WC0b01ac058001d124.
37 Carracedo-Martínez E., Pía-Morandeira A. Impacto de una alerta sanitaria sobre la utilización de ranelato de estroncio. Gac. Sanit. (2010) **24** 151–153.
38 Valiyeva E., Herrmann N., Rochon P.A., Gill S.S., Anderson G.M. Effect of regulatory warnings on antipsychotic prescription rates among elderly patients with dementia: a population-based time-series analysis. Can. Med. Assoc. J. (2008) **179** 438–446.
39 Shatin D., Gardner J.S., Stergachis A., Blough D., Graham D. Impact of mailed warning to prescribers on the co-prescription of tramadol and antidepressants. Pharmacoepidemiol. Drug Saf. (2005) **14** 149–154.
40 Piening S., Haaijer-Ruskamp F., Vries J.N. et al. Impact of safety-related regulatory action on clinical practice. Drug Saf. (2012) **35** 373–385.