

Safety Alerts: An Observational Study in Portugal

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ABSTRACT

Purpose: The information that is available when marketing authorizations are approved is limited. Pharmacovigilance has an important role during the postauthorization period, and alerts published by national authorities allow health care professionals to be informed about new data on safety profiles. This study therefore sought to analyze all safety alerts published by the Portuguese National Authority of Medicines and Health Products I.P. (INFARMED).

Methods: We conducted an observational study of all alerts published on the INFARMED website from January 2002 through December 2014. From the data included in the alerts, the following information was abstracted: active substance name (and trade name), event that led to the alert, and the resulting safety measures. Active substances were classified according to the Anatomical Therapeutic Chemical (ATC) code.

Findings: A total of 562 alerts were published, and 304 were eligible for inclusion. The musculoskeletal system was the ATC code with more alerts ($n = 53$), followed by the nervous system ($n = 42$). Communication of the information and recommendations to the health care professionals and the public in general was the most frequent safety measure ($n = 128$), followed by changes in the Summary of the Product Characteristics and package information leaflet ($n = 66$). During the study period, 26 marketing authorizations were temporarily suspended and 10 were revoked.

Implications: The knowledge of the alerts published during the postmarketing period is very useful to the health care professionals for improving prescription

and use of medicines and to the scientific community for the development of new researches. (*Clin Ther.* 2015;■■■■-■■■) © 2015 Published by Elsevier HS Journals, Inc.

Key words: pharmacovigilance, Portugal, safety alerts, National Regulatory Agency, adverse drug reactions, safety measures.

INTRODUCTION

The development process for new medicines includes preclinical and clinical studies whose objective is to evaluate their tolerability and efficacy.¹ However, the information that is available when marketing authorizations (MAs) are approved is limited. Among other limitations illustrated by the clinical trials is the fact that the population exposed to the pharmaceutical drug being studied is subject to strict inclusion and exclusion criteria, is homogenous, and does not always have similar (clinical, demographic, social, or other) characteristics to the real population.²⁻⁷ This fact is at the root of the importance of continuously monitoring the safety profiles of medicine. Thus, triggered essentially by the thalidomide phenomenon in the 1960s,⁸ pharmacovigilance systems were developed in various countries.^{4,6,9} In

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Portugal, the National Pharmacovigilance System was created in 1992.⁹

Safety profile information gathered after the medicine is placed on the market is obtained through spontaneous reporting of adverse drug reactions by health care professionals, by the MA holders, and since July 2012,¹⁰ to comply with the European directive, by patients. After spontaneous reporting, information is evaluated and coded by the pharmacovigilance systems, later being incorporated into the regulating agencies' databases.¹¹⁻¹⁶

As a result of this entire process and once the hypothesis being studied is confirmed (frequently complemented by epidemiologic evidence), a safety alert is issued by the competent regulating authorities. This contributes toward improving knowledge about the medicine's safety profile.

Thus, to evaluate the clinical information included in the published alerts, the objective of the present study is to characterize the frequency, through a code of the Anatomical Therapeutic Chemical (ATC) classification system, and the adopted measures of all the safety alerts published in Portugal by the competent regulatory authority, the National Authority of Medicines and Health Products I.P. (INFARMED), on its website.

MATERIALS AND METHODS

Research Strategy

From the INFARMED website,¹⁷ which contains the safety and quality alerts published in Portugal, alerts were selected taking into account the following inclusion criteria: (1) safety alerts; (2) alerts relative to medicines for human use; (3) alerts published from January 2002 (date when this information began to be available on the INFARMED website) through December 2014; and (4) alerts with recommendations and information released to health care professionals and the public in general (Direct Healthcare Professional Communication, changes to the Summary of Product Characteristics and the package information leaflet, suspension of MAs by a competent authority, such as INFARMED and/or the European Medicines Agency), and revocation of MAs. Exclusion criteria were as follows: (1) quality alerts; (2) alerts relative to medical devices, biosimilars, cosmetic and body hygiene products, homeopathic pharmaceutical products, and *in vivo* diagnostic devices; and (3) alerts relative to vaccines, batches,

or manufacturing and supply process and/or replenishment of supply and alerts related to MA or clinical trial processes.

Data Collection and Statistical Analysis

The following information was taken for each alert included in the analysis: publishing date of the alert on the INFARMED website, active substance name (and trade name), event that led to the alert, and the safety measures that resulting. Active substances were classified according to the ATC code.

Correlation between time and alerts publication and ATC group was assessed using nonparametric Spearman correlation coefficient r values (2-tailed). All statistical analyses were performed using SPSS statistical software for Windows, version 21.0 (SPSS Inc, Chicago, Illinois).

RESULTS

Research Results

Figure 1 illustrates the results of the research performed and of the selected safety alerts.

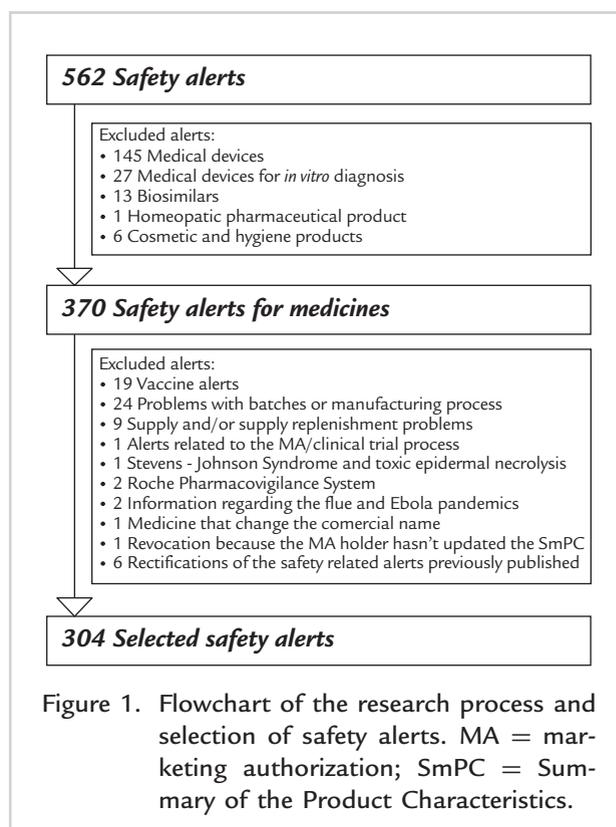


Figure 1. Flowchart of the research process and selection of safety alerts. MA = marketing authorization; SmPC = Summary of the Product Characteristics.

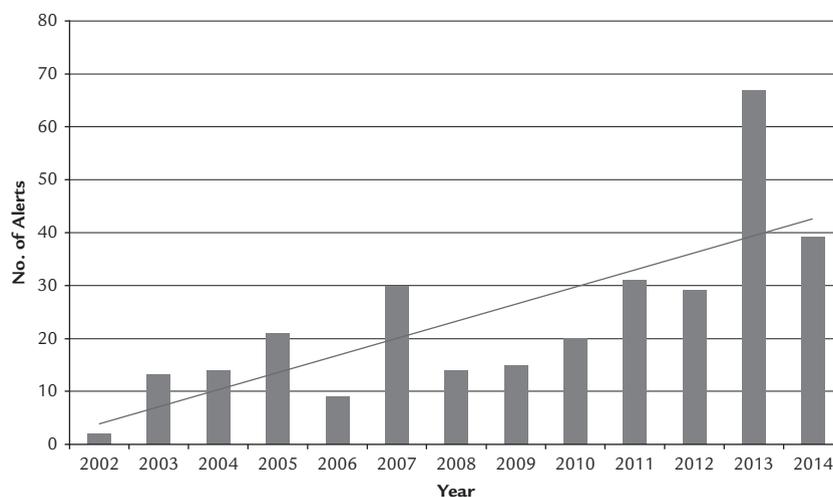


Figure 2. Yearly frequency of safety alerts published in Portugal (2002–2014).

Yearly Frequency of Safety Alerts Published in Portugal

Figure 2 shows the frequency with which selected safety alerts are published in the years considered for the study. A growing trend has been ascertained throughout time (2002–2014), as we can see in the figure with the linear tendency line. A statistical significant correlation was also found between time and alert publication ($r = 0.820$, $P = 0.001$).

Characterization of the Selected Safety Alerts by ATC Group

The number of selected safety alerts published by ATC group were as follows: A (alimentary tract and metabolism), 32; B (blood and blood-forming organs), 34; C (cardiovascular system), 29; D (dermatologicals), 5; G (genitourinary system and sex hormones), 27; H (systemic hormonal preparations, excluding sex hormones and insulins), 6; J (anti-infectives for systemic use), 22; L (antineoplastic and immunomodulating agents), 21; M (musculoskeletal system), 53; N (nervous system), 42; P (antiparasitic products, insecticides, and repellents), 1; R (respiratory system), 18; and V (various), 7. The remaining 7 safety alerts were related with the concomitant use of medicines that belong to different ATC groups.

Relative to the frequency with which safety alerts were published per ATC subgroup, the subgroups with ≥ 10 alerts are described as following: M01 (anti-inflammatory

and antirheumatic products), 36; G03 (sex hormones and modulators of the genital system), 22; A10 (drugs used in diabetes), 18; N02 (analgesics), 12; N06 (psychoanaleptics), 11; B02 (antihemorrhagics), 10; B05 (blood substitutes and perfusion solutions), 10; J05 (antivirals for systemic use), 10; L01 (antineoplastic agents), 10; L04 (immunosuppressants), 10; and M05 (drugs for treatment of bone diseases), 10.

Figure 3 illustrates the trend of safety alerts published in time for the most predominant ATC groups (>10 alerts for the period of study). Statistical significant correlation was found between time and alert publications for group A (alimentary tract and metabolism) ($r = 0.752$, $P = 0.003$), C (cardiovascular system) ($r = 0.823$, $P = 0.001$), H (systemic hormonal preparations, excluding sex hormones and insulins) ($r = 0.600$, $P = 0.03$), and L (antineoplastic and immunomodulating agents) ($r = 0.749$, $P = 0.003$).

Characterization of the Selected Safety Alerts by Adopted Safety Measure

Relative to the safety measures adopted after the publication of each of the alerts (Figure 4), it was observed that communication of the information and recommendations to the health care professionals and the public in general ($n = 128$) and changes in the Summary of the Product Characteristics and package information leaflet ($n = 66$) were the most frequent measures. In 72 of the published alerts, we verified that there were no safety

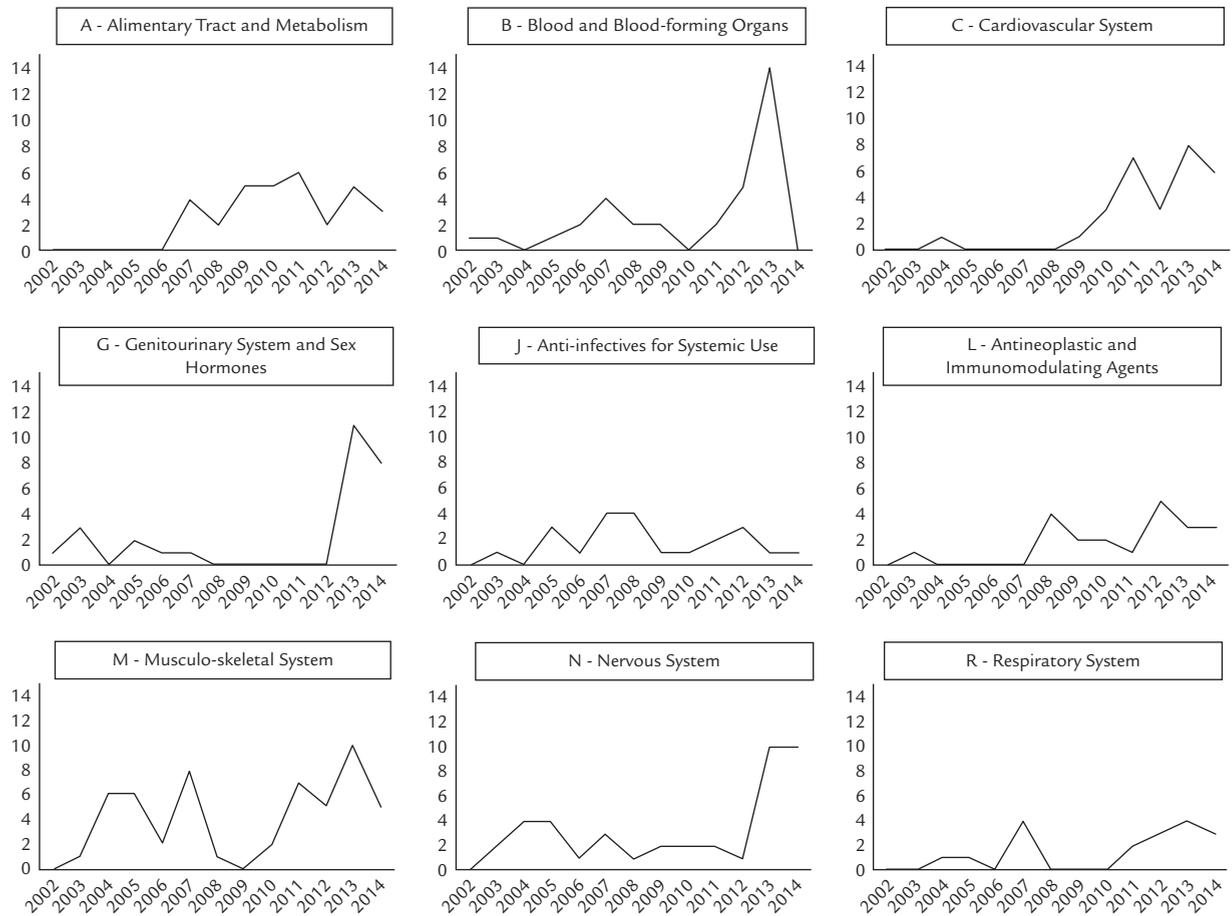


Figure 3. Trend of safety alerts published in time for the most predominant Anatomical Therapeutic Chemical groups (2002–2014).

measures taken. During this period, 26 MAs were also temporarily suspended and 10 were revoked.

DISCUSSION

This descriptive study has filled the gap relative to the absence of systematized information regarding safety alerts published in Portugal. Besides revealing the importance of monitoring after MA, the present study enables characterizing safety alerts in terms of ATC group and adopted consequential measures. The information provided should warn health care professionals of the importance of spontaneous reporting and continuous training relative to each of the medicines used in daily clinical practice. Thus, the results obtained allow reaching 3 essential conclusions.

First, safety alerts published in Portugal have increased throughout time; this fact may be related to the increasing importance given to pharmacovigilance, namely, to spontaneous reporting, by health care professionals and, in the last analysis and according to European legislation,¹⁰ by patients and the population in general. Second, some ATC groups are predominant in terms of published alerts and should be subject to special analysis, namely, in the case of anti-inflammatory and antirheumatic products (M01) ($n = 36$) that, with the known cases of nimesulide (M01AX07) or coxibs (M01AH), significantly contribute toward the frequency of alerts obtained herein. Third, the most frequent safety measure adopted was information and communication to health care professionals and the public in

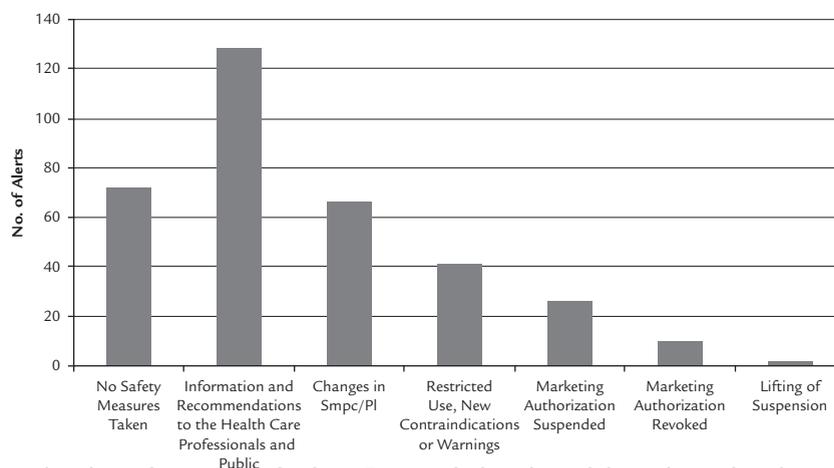


Figure 4. Frequency of safety alerts published in Portugal distributed by adopted safety measure (2002–2014). SmPC/PL = Summary of Product Characteristics and package information leaflet.

general. This finding reveals the need to warn people about the importance of disseminating this information, with expected consequences in daily practice.

No published studies were found that retrospectively characterize safety alerts throughout the years. However, some authors report the importance that knowledge of the medicine safety alerts has on prescription habits,^{18–22} revealing the importance of scientific dissemination of systematized information to health care professionals. A 10-year study in Côte d'Ivoire revealed that anti-infectious medicines had the most alerts and that the anti-inflammatory medicines were the fifth-leading medicines, with more alerts between 2001 and 2010.²³

The importance of the contribution of spontaneous reporting and the pharmacovigilance system in the creation of safety alerts to improve the safety monitoring of medicines in the postmarketing period is well indicated in this study, in which there have been recent alerts for pharmaceutical drugs that have been on the market for many years. This is the case of thiocolchicoside (M03BX05), which has been on the market for >20 years.

The most observed safety alert during the period under study was the communication of information to health care professionals and the public in general ($n = 128$). From among the categories of changes performed after issuance of an alert for a medicine, direct communication to health care professionals (Dear Doctor letter or Direct Healthcare Professional Communications) has been studied extensively by various authors.^{18,22,24–26} Some studies have reported

that a repeated safety alert has no more effect on changes to the use of a medicine than communication to health care professionals.^{18,22} There are authors that also refer that the nature of the alert can have an influence on the behavior of the prescriber at the time of selecting a medicine. An alert has less effect on prescribers, users, or caregivers when, for example, life is not at risk.^{19,20} For this reason, and taking into account that the ATC group with more alerts is also one of the groups with more sales in Portugal, it would be interesting to develop studies in the Portuguese population. Moreover the Portuguese Health Authorities could implement a monitoring program involving all physicians and pharmacists in order to identify patients that are undertaking drugs with identified safety alerts and follow-up the effects of these drugs.

Within this context, it is also important to emphasize the fundamental role that the authorities play in the release of safety alerts through direct communication to health care professionals, through their websites, through the publishing of alerts in an area of easy access, and through bulletins published periodically, such as the pharmacovigilance bulletin published quarterly by INFARMED and also available on its website.²⁷ These bulletins publish some of the alerts whose safety messages are believed to need reinforcement given that their seriousness and relevance may require a significant change in clinical practice. In the future, population-based studies should be performed to assess the consumption trends of these and other drugs with several safety alerts.

CONCLUSION

Despite all the research that takes place before a medicine is introduced to the market, within the scope of preclinical trials, experimental pharmacologic studies on animals, and clinical pharmacologic studies through clinical trials on humans, there are clinical events that are only identifiable in the postmarketing stage, when the medicine is available on the market (many times only after being marketed for several years). This finding indicates the importance of pharmacovigilance in promoting knowledge of a pharmaceutical drug's safety profile, as can be observed through this study.

It is, therefore, important that health care professional, patients, and MA holders be made aware of the need to report adverse events. Only then can a medicine's benefit-risk balance be monitored and the risks associated with medicines prevented or minimized to best protect public health.

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All authors contributed equally.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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