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Fluconazole:
Possible adverse outcomes in pregnancy

Quick Read

Due to a possible increased risk of miscarriage and stillbirths, the use of fluconazole during pregnancy should be reserved for exceptional situations, as reflected in new wording in the SmPCs of all the different formulations of fluconazole.

Fluconazole is a triazolic antimycotic agent indicated for prophylaxis and treatment of fungal infections. Its primary mechanism of action consists of inhibition of the fungal cytochrome P-450. Fluconazole is more selective for fungal than for mammalian cytochrome P-450 enzymes. It shows in vitro antifungal effect against most common species of Candida, among other fungi.

The PRAC at EMA has concluded a signal (suspected safety problem) assessment concerning the occurrence of spontaneous abortion and stillbirths with fluconazole. All the available evidence was taken into account, including the results of a patient register based cohort study (Mølgaard-Nielsen D et al, 2016)[1], other literature, and a cumulative review of cases from clinical trials and post-marketing use.

The PRAC concluded that **there is not sufficient data to justify a warning for the use of contraception** in patients using fluconazole, but as a measure to minimize the risk of spontaneous abortion and stillbirths, MA Holders are to submit changes to SmPC section 4.6 of fluconazole in all its different formulations.

4.6. Fertility, pregnancy and lactation

Pregnancy

An observational study has suggested an increased risk of spontaneous abortion in women treated with fluconazole during the first trimester. There have been reports of multiple congenital abnormalities (including brachycephalia, ears dysplasia, giant anterior fontanelle, femoral bowing and radio-humeral synostosis) in infants whose mothers were treated for at least three or more months with high doses (400-800 mg daily) of fluconazole for coccidioidomycosis. The relationship between fluconazole use and these events is unclear. Studies in animals have shown reproductive toxicity (see section 5.3).

Fluconazole in standard doses and short-term treatments should not be used in pregnancy unless clearly necessary.

Fluconazole in high dose and/or in prolonged regimens should not be used during pregnancy except for potentially life-threatening infections

Sílvia Duarte

Reference:

[1] *Association between use of oral fluconazole during pregnancy and risk of spontaneous abortion and stillbirth. Mølgaard-Nielsen D et al, JAMA 2016; 315(1); 58-67.*

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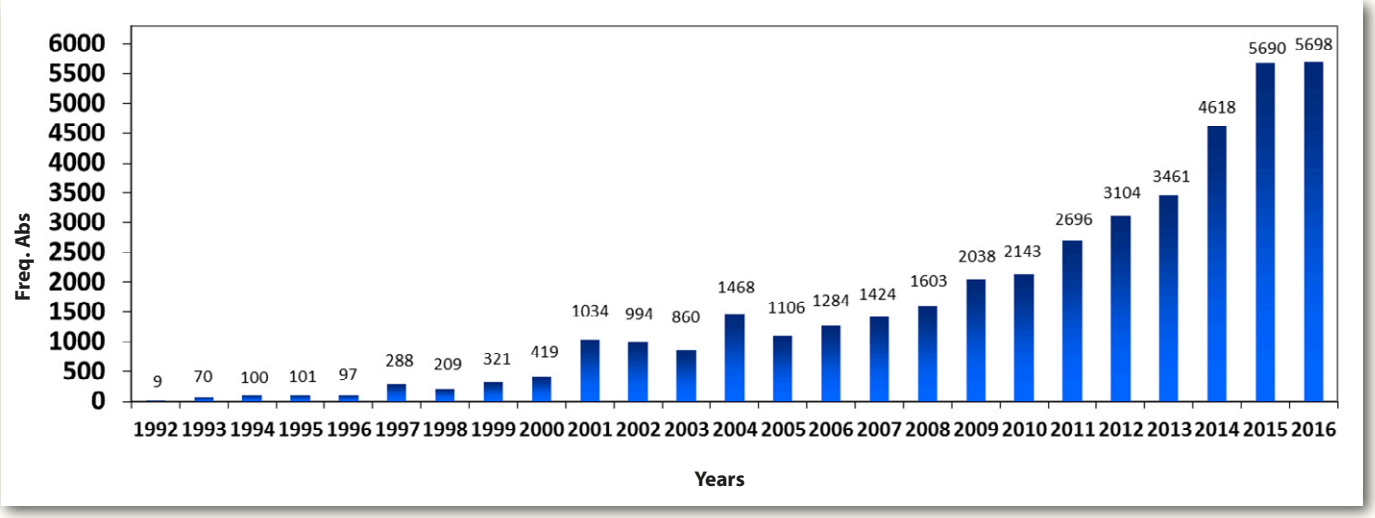
ADR Reports
Portugal 2016

Quick Read
The Portuguese National Pharmacovigilance System has reached maturity with almost 5,700 ADR reports a year.

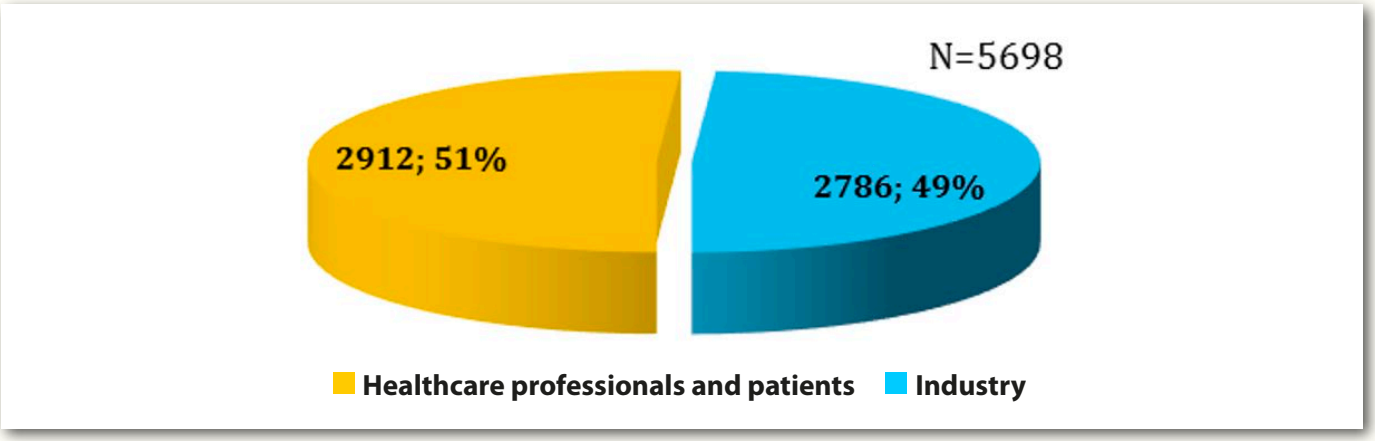
In 2016, 5,698 suspected ADR (adverse drug reaction) reports were entered into the Portuguese National Pharmacovigilance System, a peak following on constant growth since 2005 (Graph 1).



Graph 1. Annual number of suspected ADR reports received by the Portuguese National Pharmacovigilance System.

Over half of the ADR reports were made directly by healthcare professionals and consumers, while the remaining 49% came in via MA Holders, commonly known as "the industry" (Graph 2).

In the direct route (reports coming from healthcare professionals and consumers), most reports originated from physicians (38%), followed by pharmacists (26%) and consumers (11%).

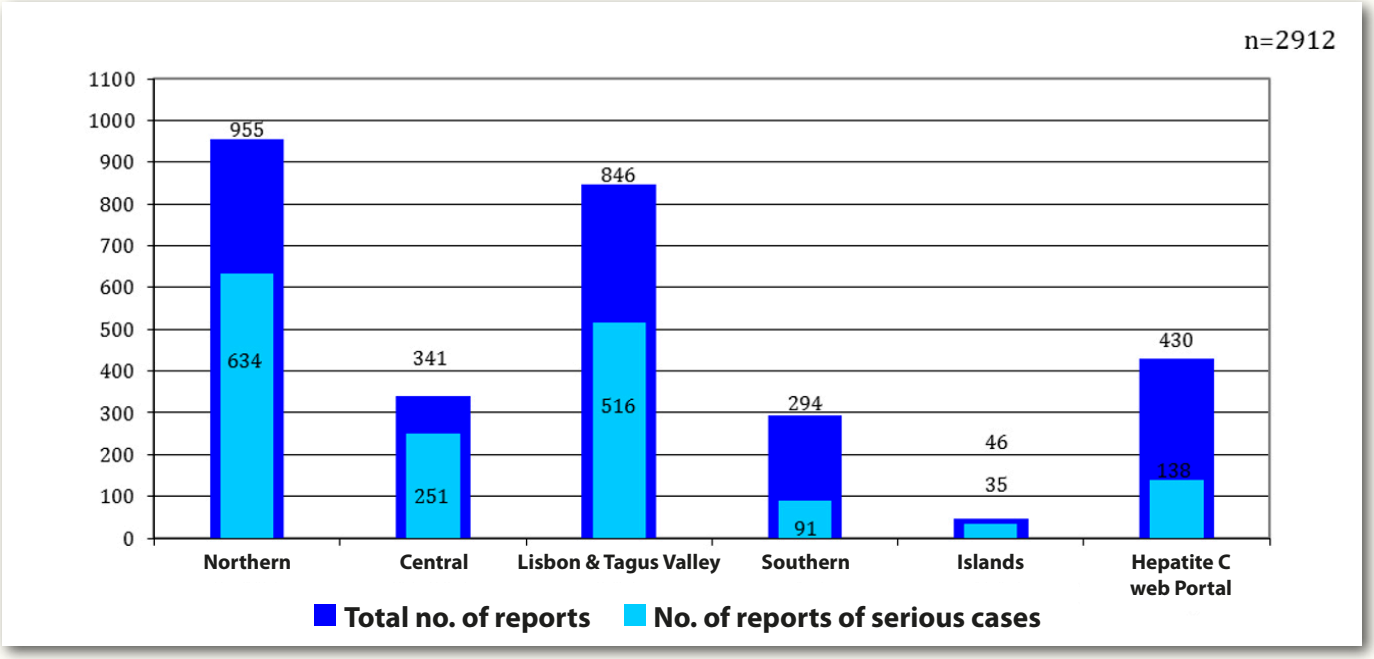


Graph 2. Suspected ADR reports received by the National Pharmacovigilance System in 2016, by type of reporting agent.

Regarding seriousness, 1,665 (57%) of reports sent in by healthcare professionals and consumers corresponded to serious reactions. This figure goes up to 99% (2,768) of the reports coming in indirectly via the industry. This very high proportion of serious reports sent by the industry was the same as in 2015. This is not unexpected since regulations in place, with few exceptions, only require MA Holders to report serious ADRs.

Graph 3 overleaf shows the geographical* distribution of the 2,912 reports received directly from healthcare professionals and consumers, as well as the proportion of serious reports.

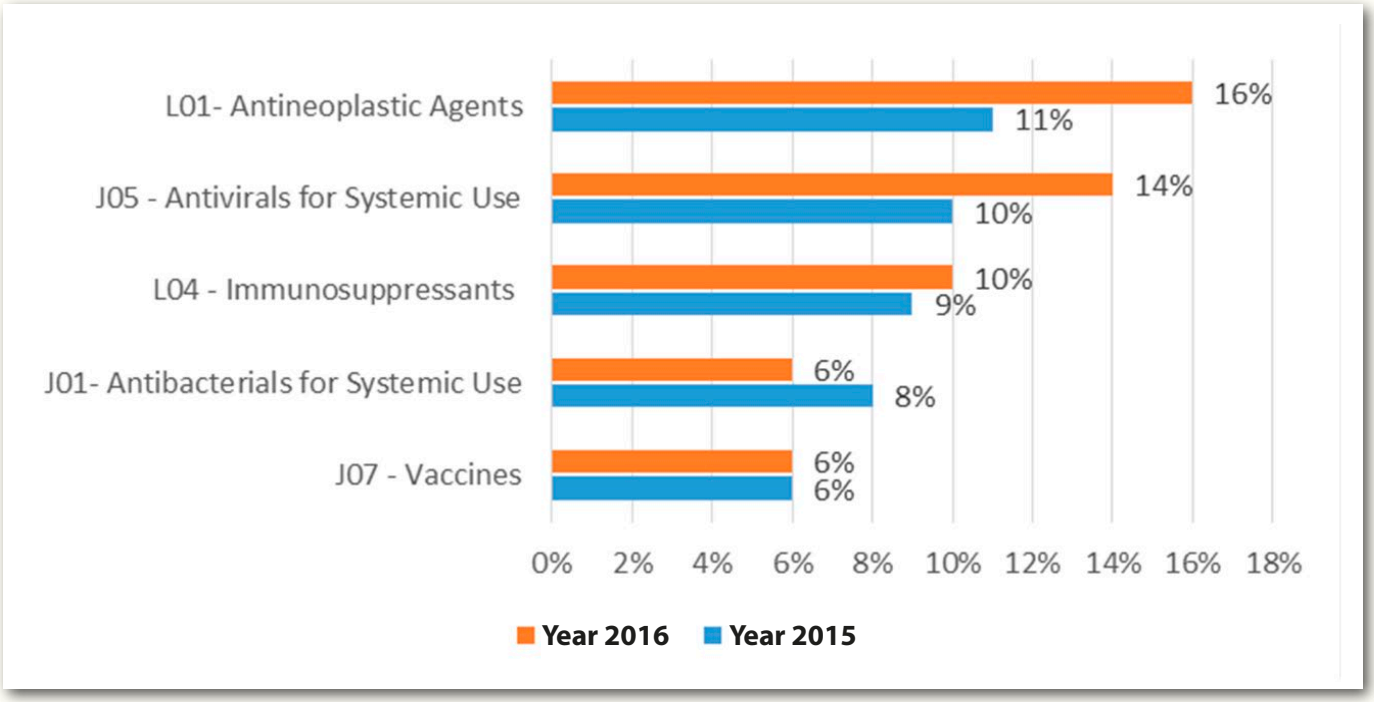
** The Portuguese National Pharmacovigilance System changed on 1 January 2017 to be made up of INFARMED I.P.'s Medicines Risk Management Dpt (the head of the System and also the unit in charge of processing ADR reports from the Azores and Madeira islands and a number of Lisbon region municipalities' catchment areas) and seven Regional Pharmacovigilance Units: Porto, Coimbra, Lisbon, Setúbal & Santarém, Guimarães, Beira Interior, and Algarve & Alentejo. This setup did not yet exist in 2016.*



Graph 3. ADR reports from healthcare professionals and consumers received by the Portuguese National Pharmacovigilance System in 2016, by region of origin and seriousness criteria.

To further break down the ADRs into categories, the system organ groups for each suspected ADR were determined. These groups correspond to MedDRA (Medical Dictionary for Regulatory Activities) hierarchical level Primary SOC (System Organ Class) terms. Of all the cases put together, the following SOCs predominate: **General disorders and administration site conditions, Skin and subcutaneous tissue disorders, Gastrointestinal disorders** and **Nervous system disorders**. Those four SOCs alone correspond to **48%** of reports, whereas the remaining 52% are distributed across as many as 22 different SOCs.

The ATC (Anatomical Therapeutic Chemical) classes were also determined for the suspect or interacting drugs implicated in the ADR cases. The five most represented ATC groups in 2016 accounted for 52% of all reports (Graph 4). This was the same pattern as in 2015 in which **antineoplastic and antiviral agents** also stood out. These two drug groups include medicines from therapeutic fields that are the object of intensive innovation and which are indicated in usually complex, polymedicated conditions.



Graph 4. The five most frequently implicated ATCs in ADR reports received in 2016 by the Portuguese National Pharmacovigilance System (53% of the total (N=3,454)).

António Leandro Ponte, Leonor Nogueira Guerra

ADRs in the Literature

How the risk-benefit ratio of a new medicine is perceived may be influenced by patients' numeracy and the way information is conveyed.

The sequence and amount of information given to patients both influence their perception of risk. As opposed to most previous studies assessing patients' risk perception from their reading of written materials, this study looked at the effect of various oral communication strategies regarding a new medicinal product on patients of variable numeracy level.

Perception of the value of the new medicine was measured by asking the 389 participants in the study to indicate, after listening to a randomly assigned oral version, whether risks outweighed benefits, whether they were balanced or, on the contrary, whether benefits outweighed risks.

According to the authors of the study, the results suggest that, in the case of patients with average to high subjective numeracy, the value of medicines is perceived as higher (benefits outweighing risks) when an extensive briefing on adverse effects follows a short presentation of the benefits. Other communication strategies, including giving more information on benefits, did not result in such a positive perception in patients with average to high numeracy.

Subjective Numeracy and the Influence of Order and Amount of Audible Information on Perceived Medication Value. Fraenkel L et al. Medical Decision Making Vol 37, Issue 3, 2017.

Educational Materials published in the Infomed product information webpage

Medicinal product (DCI)	Click on the links (in Portuguese)
Abacavir + Lamivudina Mylan (abacavir + lamivudine)	***Educational materials for healthcare professionals*** Reações de Hipersensibilidade (RHS) associadas ao Abacavir – 1.ª Versão For all physicians experienced in HIV treatment, hospital infectious diseases and internal medicine department heads, as well as heads of hospital pharmaceutical services. Published on 29-03-2017

Compiled by Magda Pedro

What do they mean?

ADR	Adverse Drug Reaction
EMA	European Medicines Agency
MA	Marketing Authorization
PIL	Patient Information Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee (EMA)
SmPC	Summary of Product Characteristics