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Online Adverse Drug Reaction Reports increase exponentially with new ADR Portal

On 22 November 2017 INFARMED's **new ADR Portal** went live. Reporting suspected ADRs to the agency has become easier and faster for healthcare professionals and consumers who can play an active role in continuously monitoring the safety and benefit/risk of medicinal products.

Several National Pharmacovigilance System information campaigns were put in place to make both healthcare professionals and citizens aware of the new portal's more user-friendly interface, in an effort to address the causes of underreporting such as lack of time, reporting complexity and difficulty in accessing reporting tools.

A very significant increase in online reports can already be seen, as shown by the comparative data from the pre-new ADR Portal and immediately post-new ADR Portal phases. For this comparison the reference periods were 01-08-2017 to 30-11-2017 (pre-Portal period[1]) and the post-Portal period from 01-12-2017 to 31-03-2018. Figure 1 shows how online reporting soared in every region in the country in the post-portal period.

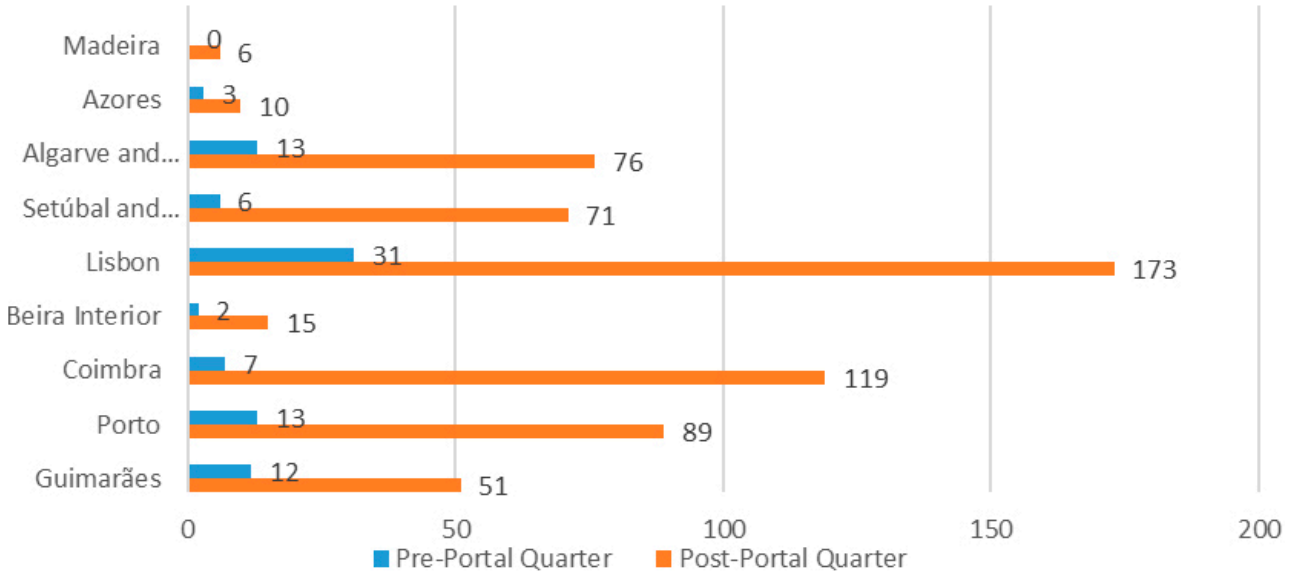

Figure 1.
Total number of online reports (absolute frequency): comparison of the pre- and post-new ADR Portal periods.

[1] *Since the new ADR Portal went live near the end of the month of November, all the data pertaining to 11-2017 were included in the "pre-portal 4-month period".*

INDEX CARD

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Online Adverse Drug Reaction Reports increase exponentially with new ADR Portal (cont'd)

Eighty-seven reports were entered online in the pre-Portal period and as many as 610 in the four months post-Portal. This significant growth concerned both consumers and healthcare professionals (Figure 2).

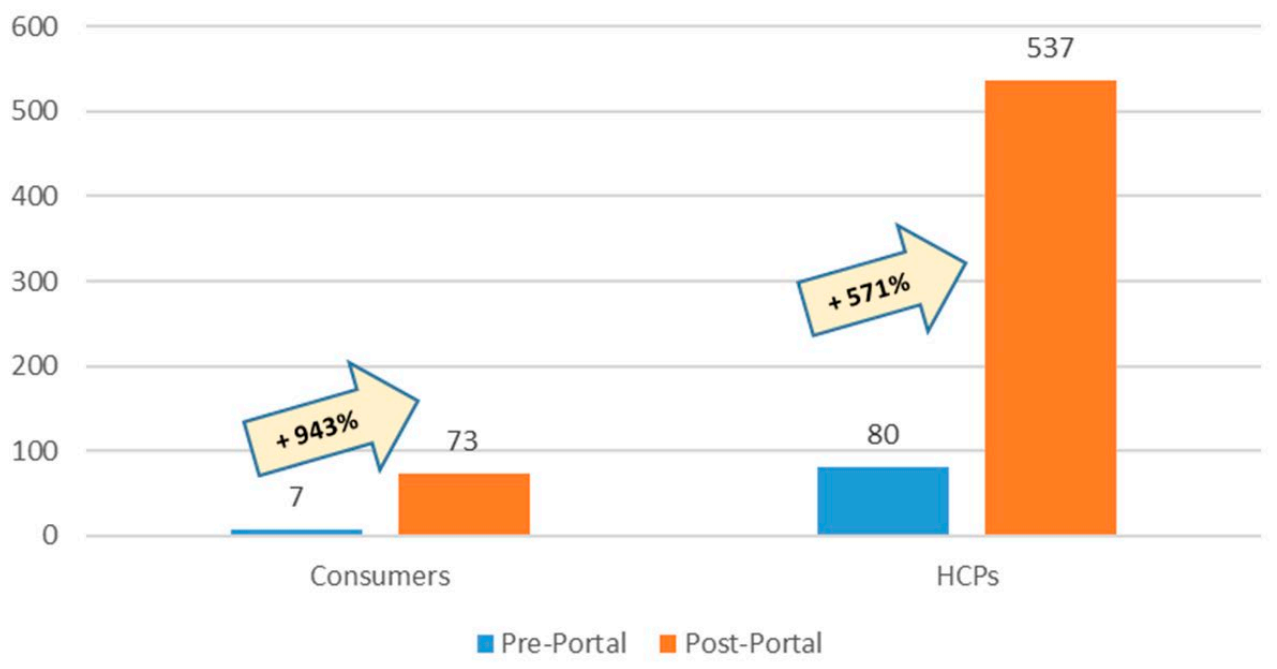


Figure 2. Online reports in the pre- and post-new ADR Portal periods: variation by type of reporter.

Adverse drug reaction reports are expected to go on increasing and mostly so through the electronic route.

INFARMED will keep promoting diverse means of communication and contents to motivate professionals and citizens in general to participate in a knowledge network that aims to make medicines ever safer.

Leandro Ponte, Leonor Nogueira Guerra

Portal **RAM**

Notificação de Reações Adversas a Medicamentos

Report an adverse drug reaction here.

Find answers to your questions about the ADR Portal here.

Tramadol oral solution:
Minimizing the risk of accidental overdose with the dosing pump

Quick Read

Each drop from the Tramal® oral solution dropper contains 2.5 mg of tramadol hydrochloride, whereas each full activation of the dosing pump gives 12.5 mg of tramadol hydrochloride, i.e., a 5-fold higher dose. This equivalence should always be borne in mind to avoid accidental overdosing. Several measures have recently been taken accordingly.

Tramadol, a centrally-acting opioid pain killer, is a pure, non-selective agonist of opioid receptors miu (μ), sigma (δ) and kappa (k), with greater affinity for μ receptors. Neuronal noradrenalin reuptake inhibition and increased serotonin release also contribute to its analgesic effect.

Products containing tramadol in solution, oral drop form are indicated for the treatment of moderate to severe pain. They are marketed in Portugal in droppers (10 ml, 30 ml) or in bottles with a dosing pump (30 ml).

Cases of accidental overdose with Tramal, 100 mg/ml, oral solution, in 30-ml bottles with a dosing pump, have been reported. These accidents resulted from medication errors having to do with the fact that there are **two different pharmaceutical presentations**: dropper bottle and bottle with dosing pump.

The amount of medicine given by each is not the same, in that **each drop from the dropper contains 2.5 mg of tramadol hydrochloride, whereas each full activation of the dosing pump gives 12.5 mg of the active ingredient (five times more)**.

In order to minimize the risk of yet more cases of overdose, the MA holder of Tramal® articulated with INFARMED a set of preventive measures:

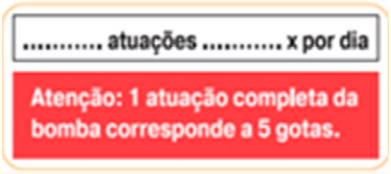
→ Information to healthcare professionals and the public to make it clearer that one activation of the dosing pump does not correspond to one drop from the dropper. The equivalence goes as follows:

1 full activation of pump = 5 drops = 12.5 mg = 0.125 ml

→ Alert notices sent out to prescribing physicians and pharmacists who should educate their patients on the correct posology, by laying out a direct equivalence between drops and pump activations.

- Circular Informativa N.º 153/CD/550.20.001, de 22 de novembro de 2017
- Comunicação dirigida aos Profissionais de Saúde.

→ Voluntary suspension by the MA holder of the marketing of Tramal in 30-ml bottles with a dosing pump until a label is included with a dosing equivalence alert:



→ Change in labelling, PL and SmPC to permanently include the equivalence between pump activations and number of drops.

→ Reintroduction in the market of Tramal 10-ml bottle with dropper, to cover for the need of paediatric dosing.

The cooperation of all healthcare professionals is essential in educating patients and in reporting any adverse reactions they may come across or be made aware of. The MA holder and INFARMED will keep monitoring this issue to assess the effectivity of the above measures.

Ana Severiano

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

Ritonavir and fixed-dose combinations:
Interaction that may decrease the effect of Levothyroxine

Quick Read

The effect of levothyroxine may be decreased by an interaction with ritonavir. Patients on levothyroxine therapy should have their thyroid function assessed when ritonavir is started and/or when it is discontinued.

Ritonavir is a protease inhibitor indicated, in combination with other antiretrovirals, in the treatment of patients (adults and children 2 years of age or older) with HIV-1 infection. It is largely metabolized by the liver cytochrome P450 system, mainly by the isoenzyme CYP3A family and, to a lesser extent, by the CYP2D6 isoform. Low doses of ritonavir have significant effects on the pharmacokinetics of other protease inhibitors and of drugs metabolized by CYP3A4.

Levothyroxine is metabolized by deiodination and glucuronidation. L-thyroxine (T4) is converted into L-triiodothyronine (T3) in the blood by shedding one iodine atom, which makes it three-fold more efficient in activating the thyroid-specific intracellular receptors.

Ritonavir can induce glucuronidation of drugs such as levothyroxine, thus increasing their biotransformation and decreasing their systemic exposure, which can stunt their therapeutic effect.

Eighteen cases of a possible levothyroxine-ritonavir (or fixed-dose combination ritonavir+lopinavir), have been reported, including literature cases (Berger JL et al 2017; Ruellen A et al, 2011; Sahajpal R et al, 2017; Touzot A et al, 2006).

The PRAC at EMA concluded that an interaction between levothyroxine and protease inhibitors leading to loss of therapeutic effect of the former, cannot be excluded. An update to the corresponding product information was therefore recommended. The SmPCs of medicinal products containing ritonavir or fixed-dose combinations (namely ritonavir, lopinavir / ritonavir, ombitasvir, paritaprevir), as well as of the SmPC of products containing levothyroxine whose section 4.5 does not mention the possibility of interaction with protease inhibitors, will read:

4.5. Interaction with other medicinal products and other forms of interaction

Post-marketing cases have been reported indicating a potential interaction between ritonavir containing products and levothyroxine. Thyroid-stimulating hormone (TSH) should be monitored in patients treated with levothyroxine at least the first month after starting and/or ending ritonavir treatment.

Elsa de Fátima Costa

Communications to Healthcare Professionals published on the Infarmed website

Click on the links.

INN Medicinal product	Target	Comunication Online publication date
Levetiracetam – oral solution Keppra Levetiracetam: Actavis Group, Alter, Aristo, Aurovitas, Bluefish, Bluepharma, Ciclum, Cinaz, Cinfa, Farmoz, Generis, Jaba, Labesfal, Mepha, Ratiopharm, Sandoz, Tecnigen, Teva, Tirbas, Tolife, UCB, Zentiva	**Physicians:** paediatricians and paediatric neurologists. **Pharmacists**	**Risk of medication errors causing accidental overdose** 02-04-2018
Flupirtine Metanor	**Physicians:** general/family doctors, orthopaedic surgeons, neurologists, internists, sports medicine physicians, occupational physicians, rheumatologists, and rehabilitation medicine physicians. **Pharmacists:** community.	**Metanor, 100 mg, capsule – European revocation of the MA of flupirtine-containing products** 04-04-2018

Compiled by Fernanda Marques