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Flupirtine withdrawn

Quick Read

Due to a risk of serious liver toxicity the benefit-risk of flupirtine-containing products is no longer deemed favourable. The corresponding marketing authorisations have consequently been revoked and those products will no longer be available in the European Union market.

Flupirtine is a centrally acting non-narcotic analgesic and a SNEPCO (Selective NEuronal Potassium Channel Opener) prototype. Serious liver adverse reactions are of special relevance in its safety profile.

Flupirtine, which is authorised in Portugal since the 1990s, underwent a European safety review earlier in **2013** on account of a risk of serious hepatotoxicity. As a consequence of this assessment, **restrictions** were then imposed to flupirtine-containing products. Their market authorisation became limited to the treatment of acute pain in adults with a maximum duration of two weeks and only when therapy with other analgesics (e.g., non-steroidal anti-inflammatory agents or weak opioids) was contraindicated. Weekly liver function monitoring also became necessary.

In October **2017** a new safety review was started in that the above restrictions were not being adequately put into clinical practice and cases of serious liver injury were still being reported, including acute liver failure with a fatal outcome or requiring a liver transplant. This assessment review could not identify any measures that would result in greater compliance with the defined safety restrictions or in adequate hepatotoxicity risk reduction.

The PRAC at EMA took into account the failure of previous measures (six observational studies showed a substantial degree of non-compliance with previously determined safety restrictions), the absence of risk factors which could be sufficiently sensitive to predict the occurrence of significant liver toxicity, as well as the clinical setting in which these medicines are used. It was concluded that the risk of hepatotoxicity outweighs the benefits of flupirtine-containing products and a recommendation was made that their MAs be revoked in all the European Union.

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Over 220,000 adverse drug reaction reports recorded in Portuguese hospitals between 2000 and 2015

The authors of this article recently published in the Journal of Medical Systems looked into the Homogeneous Diagnosis Groups (HDG) database in the 2000-2015 period to estimate the frequency and impact of adverse events in Portuguese state-run hospitals.

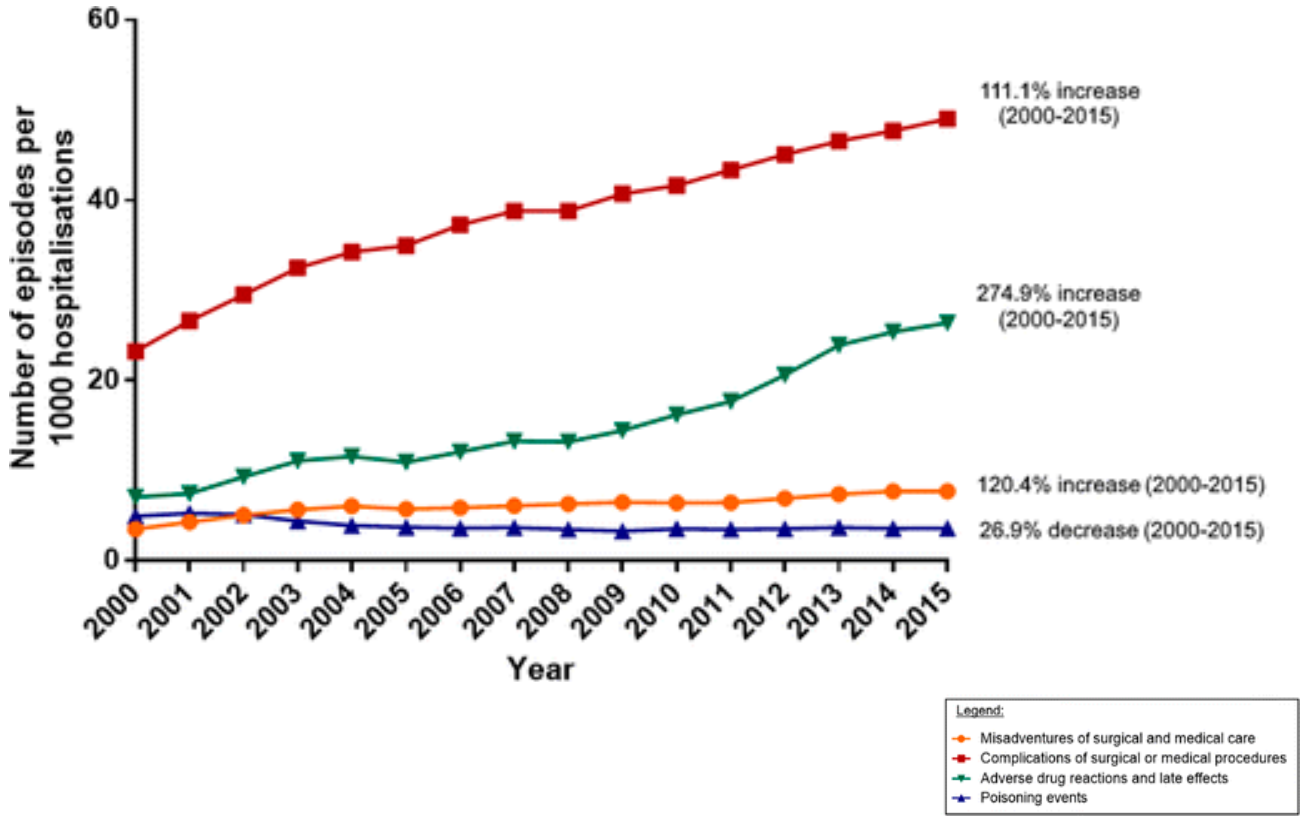
Adverse events were subdivided into 5 types (Table) and the corresponding ICD-9-CM (International Classification of Diseases) codes were identified.

	Type of adverse event	Definition
1	**Misadventures** in provision of medical or surgical care	Adverse event occurring while care is being provided, caused by the professional or the procedure.
2	**Complications** arising from provision of medical or surgical care	Abnormal reactions caused by the medical or surgical procedure (but no incident recorded).
3	**Poisoning**	Events resulting from accidental medicinal overdose, administration of wrong substance, inadvertent use of medicines, and accidents from the use of medicines in medical or surgical procedures.
4	**Adverse drug reactions (ADRs)**	Harmful and undesirable effects occurring in doses normally used in humans for prophylaxis, diagnosis, therapy or modification of physiological functions. This definition excludes overdose and abuse.
5	**Late effects**	Events occurring as the natural evolution of the acute stage of other events.

Analysis of 15 million hospital hospitalisations in the study period revealed that around 860,000 of those hospitalisations (5.8% of total) had at least one associated adverse event and that around 220,000 (1.5% of total) had at least one associated adverse drug reaction. The financial impact of the total of adverse events and associated costs was estimated to be 4.8 billion euros within the timeframe studied.

Also of importance is the fact that the types that contributed most towards the high number of recorded adverse events were complications from medical and surgical procedures and adverse drug reactions (see Figure). Both have shown an upward trend since 2000 (though this may partly be due to improvements in the HDG system).

Number of adverse events recorded annually, by type and per 1000 hospitalisations (Continental Portugal, 2000–2015).



The number of ADRs in this study is over six times higher than the number of ADRs reported to the National Pharmacovigilance System in the same period (2000-2015), which was around 34,000.

Although the HDG database has methodological limitations to do with the fact that it was originally designed for administrative purposes in relation to hospital care provision payments, and not as a clinical information system, the results obtained seem to indirectly confirm that underreporting of ADRs in Portugal is a significant phenomenon.

Frequency and impact of adverse events in inpatients: a nationwide analysis of episodes between 2000 and 2015. Sousa-Pinto B et al. J Med Syst (2018) 42: 48. **https://doi.org/10.1007/s10916-018-0898-5 .**

Miguel Antunes

Communications to Healthcare Professionals published on the Infarmed website

Click on the links.

INN Medicinal product	Target	Comunication Online publication date
Radium (223Ra) dichloride Xofigo	**Physicians:** : oncologists (specialists in prostate cancer), urologists (specialised in prostate cancer) and nuclear medicine specialists. **Pharmacists:** pharmaceutical services in hospitals with nuclear medicine units.	Radium 223 dichloride (Xofigo) contraindicated in association with abiraterone acetate and prednisone/prednisolone. 26-03-2018

Compiled by Magda Pedro

Educational Materials published in the Infomed product information webpage

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INN Medicinal product	Target	Materials Online publication date
Etanercept Enbrel – only for injectable solution in pre-filled pen	**Physicians:** rheumatologists, internists and dermatologists. **Nurses:** in clinics dealing with rheumatoid arthritis, juvenile idiopathic arhtritis, ankylosing spondilitis, psoriatic arthritis and psoriasis, axial spondiloarthritis without radiographic changes, and paediatric plaque psoriasis patients; patient home training programmes. **Pharmacists:** hospital (departmental heads or directors).	Detailed guide on adequate technique
	Patients	Detailed guide on adequate technique Instruction video on use of MYCLIC pre-filled pen 28/03/2018
Levodopa + Carbidopa Duodopa	**Physicians:** gastroenterologists. **Nurses:** in gastrenterology departments caring for patients receiving Duodopa therapy.	Presentation on critical PEG/J preparation, placement and post-operative care aspects
	Patients	Pocket guide 05/03/2018
Tocilizumab RoActemra	**Physicians:** internists, rheumatologists and paediatricians. **Nurses**	Safety information on the treatment of patients with rheumatoid arthritis and giant cell arteritis
	Patients	Brochure for patients with giant cell arteritis (applicable only to the injectable SC solution) Alert card 05/03/2018
Tofacitinib Xeljanz	**Physicians:** prescribers.	Start of treatment checklist Maintenance treatment checklist Safety information guide
	Patients	Alert card 28/03/2018
Voriconazole Voriconazol Aurovitas Voriconazol Accord Voriconazol Fresenius Kabi Voriconazol Normon Voriconazol Teva	**Physicians:** infectious diseases specialists, haematologists, dermatologists, oncologists.	Q&A brochure Checklist
	Patients	Alert card 28/03/2018

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