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ADRs in the Literature
Medication-associated hospitalization

Medication-associated adverse events - from medication errors and accidental off-label use to adverse drug reactions in the strict sense - often cause untoward effects in patients. Some of the consequences of those effects are preventable, including a proportion of cases of hospital admission.

In this Australian study, which used a mixed literature, clinical record and administrative data review methodology, researchers estimated a **median annual incidence of medication-related hospital admissions of 2.5%**. Two thirds of those hospitalizations were estimated to be preventable.

Looking at the 2019 Continental Portugal figures of a total of 810,900 hospital admissions, and applying the proportion found in this study, one comes to a potential estimate of over 20 thousand annual cases of hospitalization in this country whose cause was related to medicines.

• Lim R et al. The Extent of Medication-Related Hospital Admissions in Australia: A Review from 1988 to 2021. Drug Saf. 2022 Mar;45(3):249-257.

•https://www.pordata.pt/Portugal/SNS+consultas++internamentos+e+urg%C3%AAncias+++Continente-159

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ADRs in the Literature
Fever of Unknown Origin caused by Medicines

Fever of Unknown Origin (FUO) is not a condition per se but rather a clinical manifestation that is common to various pathological processes.

The definition of FUO follows variable and heterogeneous criteria namely in what regards the period of time to be considered and the diagnostic parameters to be included. However, one commonly accepted definition stipulates a body temperature of 38.3ºC or higher, lasting for over 3 weeks despite comprehensive diagnostic investigation.

Among the ultimate causes of FUO, adverse drug reactions **(ADRs)** amount to circa **3 to 7% of cases prompting hospitalization.**

The following table (adapted from the original table in this New England Journal of Medicine review article) categorizes the medicinal causes of FUO. Hyperthermia syndromes are a rare but extremely severe subclass of causes.

Type of ADR	Usual run-in time between start of exposure to the drug and onset of fever	Medicines commonly involved
Hypersensitivity reaction	7 - 10 days	Antibiotics, allopurinol, anticonvulsants, etc
Chemotherapy-related reaction	7 - 10 days	Chemotherapeutic agents
Infusion-related reaction	30 minutes – 3 hours	Amphotericin B, vancomycin, bleomycin, vaccines, monoclonal antibodies
DRESS (drug-reaction with eosinophilia and systemic symptoms)	2 - 6 weeks	See here
Hyperthermia syndromes		
Serotoninergic syndrome	6 hours – several days	SSRIs, SNRIs, tricyclic antidepressants, MAO inhibitors, antiemetics (ondansetron, metoclopramide), serotonin receptor agonists (psychedelics such as LSD, fentanyl, buspirone, triptans, lithium), medicinal herbs such as St John's wort (which potentiates SSRIs) or harmine/harmaline (MAO inhibitor), cytochrome P-450 inhibitors (fluoxetine, ciprofloxacin, ritonavir, fluconazole, sertraline)
Malignant hyperthermia	30 minutes – 2 hours	Depolarizing muscle relaxants (succinylcholine), inhaled anaesthetics
Malignant neuroleptic syndrome	1 – 2 weeks	Antipsychotics, antiemetics (metoclopramide, prochlorperazine), abrupt discontinuation of dopamine agonists or of non-dopaminergic agents (amantadine)
Adrenergic fever	variable	Sympathomimetics and MAO inhibitors (theophylline, cocaine, MDMA (ecstasy))
Anticholinergic fever	around 2 hours	Anticonvulsants, antiemetics, muscle relaxants, etc
Mitochondrial oxidative phosphorylation decoupling	30 minutes – 3 hours	Pesticides and toxins (organochlorides, snake venom derived phospholipases), acetylsalicylic acid in high doses

• Haidar G, Singh N. Fever of Unknown Origin. N Engl J Med. 2022 Feb 3;386(5):463-477

Excipients: safety information in patient leaflets – part 6
G, H

Excipient	Route(s) of administration	Information in Patient Leaflet	Comments
Galactose	oral, parenteral	*If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.* *Contains x g galactose per dose. This should be taken into account in patients with diabetes mellitus.*	• Patients with rare hereditary problems of galactose intolerance, e.g. galactosaemia or glucose-galactose malabsorption, should not take galactose-containing products.
Glucose (dextrose)	oral, parenteral	*If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.* *Contains x g glucose per dose. This should be taken into account in patients with diabetes mellitus.*	• Widely used in solutions for tonicity adjustments and as a sweetening agent. Also used as a diluent and a binder for tablets, especially chewable tablets. • Patients with rare glucose-galactose malabsorption should not take glucose-containing products. • Information on dental prophylaxis to be included only when the medicinal product may be intended for chronic use, e.g., for two weeks or more.
	oral liquids, lozenges and chewable tablets	*May be harmful to teeth*	
Glycerol (E 422) (glycerine)	Oral	*May cause headache, stomach upset and diarrhoea.*	• Used as a solvent or a co-solvent. It is also a sweetening agent. Used as a gelatin plastifier in soft capsules and suppositories. • Food additive.
	rectal	*May have a mild laxative effect.*	
Heparin (as excipient)	parenteral	*May cause allergic reactions and reduced blood cell counts which may affect the blood clotting system. Patients with a history of heparin-induced allergic reactions should avoid the use of heparin-containing medicines.*	• As a glycosaminoglycan, it potentiates the action of non-steroidal anti-inflammatory drugs in plaster formulations.

Communications to Healthcare Professionals published on the Infomed product information webpage
Click on the links.

INN Medicinal product	Target	Communication Online publication date
Infliximab *Flixabi* *Inflectra* *Remicade* *Remsima* *Zessly*	**Physicians:** internists, rheumatologists, gastroenterologists, dermatologists, paediatricians and obstetricians	**Use of live vaccines in infants who have been exposed in utero or through breastfeeding** 09-03-2022

Compiled by Patrícia Catalão

Educational Materials published on the Infomed product information webpage

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INN Medicinal product	Target	Materials Online publication date
Axicabtagene ciloleucel *Yescarta* **Autologous anti-CD19 -transduced CD3+ cells** *Tecartus*	**Healthcare professionals:** multidisciplinary teams at qualified centres in charge of patients on therapy with Yescarta and Tecartus	Guide for healthcare professionals on handling and administration, and recommendations regarding collection of samples of secondary malignancies Guide for healthcare professionals on management of cytokine release syndrome and of serious adverse neurological reactions 03-03-2022
Deferasirox *Deferasirox Teva*	**Physicians:** immunohemotherapy specialists, haematologists and paediatricians **Patients**	Guide for healthcare professionals Guide 05-03-2022
Emtricitabine + tenofovir *Emtricitabina + tenofovir disoproxil Zentiva* *Emtricitabina + tenofovir Zentiva*	**Physicians:** potential PrEP prescribers, namely infectious diseases and internal medicine specialists **Patients**	Important safety information for prescribers regarding pre-exposure prophylaxis (PrEP) Checklist for the prescribing physician Important information for reduction of the risk of acquiring HIV infection – PrEP Reminder card 24-03-2022
Emtricitabine + tenofovir *Emtricitabina + tenofovir* Teva **Tenofovir** *Tenofovir Teva*	**Physicians:** infectious diseases specialists, internists, gastroenterologists and paediatricians	Important safety information for prescribers on renal function monitoring and dose adjustment in adolescent patients with chronic hepatitis and/or HIV infection 24-03-2022
Fingolimod *Fingolimod Mylan*	**Physicians:** neurologists and neuropaediatricians **Patients**	Checklist Guide for patients, parents and caregivers Specific pregnancy alert card 23-03-2022
Fingolimod *Fingolimod Generis* *Fingolimod Medochemie* *Fingolimod Zentiva*	**Physicians:** neurologists, neuropaediatricians and gynaecologists/obstetricians **Patients**	Checklist Guide for patients, parents and caregivers Specific pregnancy alert card 23-03-2022

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Educational Materials published on the Infomed product information webpage

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INN Medicinal product	Target	Materials Online publication date
Isatuximab *Sarclisa*	**Physicians:** oncologists, haematologists and immunohemotherapy departments treating patients with multiple myeloma **Patients**	Guide for healthcare professionals and blood banks Alert card 24-03-2022
Nitric oxide *Nomixgen*	**Healthcare professionals:** physicians and nurses at hospital neonatology, paediatric and cardiothoracic ICU units	Guide for healthcare professionals 31-03-2022
Ravulizumab *Ultomiris*	**Physicians:** haematologists **Patients**	Guide for the prescribing physician – PNH Guide for parents - aHUS and PNH Guide for patients - PNH Paediatric patient alert card (aHUS and PNH) 14-03-2022
Teriflunomide *Aubagio*	**Physicians:** neurologists **Patients**	Guide Card 23-03-2022

Compiled by Patrícia Catalão

What do they mean?

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