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Biologicals

Quick Read

The trademark name and the batch used, among other data, are indispensable for the analysis of cases of suspected adverse reactions to biological medicinal products.

Biologicals are medicinal products whose active substance is produced or extracted from a biological source. They include ***blood and plasma-derived products, biotechnological medicines, vaccines*** *and advanced therapy medicines (****genetic*** *therapy, therapy with* ***somatic cells*** *and* ***tissue engineering****).*

The quality profile of biologicals is dynamic and varies according to manufacturing process. It is therefore essential to ensure their **traceability** at every level of production, namely through their **trademark name and batch number**.

A search undertaken on the **Portal RAM**, encompassing the period from January 2018 to March 2019 has shown that 35% of reports (611 of a total of 1,757) of adverse reactions to biologicals did not include a trademark name or a batch number. Some reports did contain the batch number in the narrative, though not in the corresponding structured field, which suggests some lack of knowledge on how to adequately fill out an ADR report form. In a significant number of reports the data initially provided was not satisfactory and no evidence of follow-up was found.

In order to minimize this problem, Infarmed has published an Information Circular: ***Reporting ADRs to Biological Medicinal Products – Information on Trademark Name and Batch Number***. Marketing Authorization Holders (MAHs) have also been approached on this issue. MAHs have identified the following as the main reasons for data insufficiency:

- batch number cannot be retrieved because healthcare professional or consumer has discarded the package;
- primary reporting person cannot be contacted for follow-up and for obtaining any missing data;
- in the case of literature reports this type of data is missing and cannot be retrieved.

It is important to keep in mind:

- Reporting health professionals: trademark name and batch number are essential for adequate assessment of ADRs associated with biological medicinal products.
- MAHs: whenever important case data is missing, a request for additional information from the primary reporting source should be ensured.

Beatriz Tanoeiro and Maria João Jesus

INDEX CARD

Director: Fátima Canedo
Editor: Rui Pombal
Contributors: Ana Severiano, Ana Sofia Martins, Cristina Mousinho, Elsa de Fátima Costa, Fátima Bragança, Fátima Hergy, Fernanda Marques, Magda Pedro, Márcia Silva, Miguel Antunes, Sílvia Duarte
Publishing Assistant: Inocência Pinto
Advisory Board: Conselho Diretivo do INFARMED, I.P.
INFARMED – Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.
Parque de Saúde de Lisboa, Av. do Brasil, N.º 53, 1749-004 Lisboa
Phone: +351 217 987 100
E-mail: farmacovigilancia@infarmed.pt
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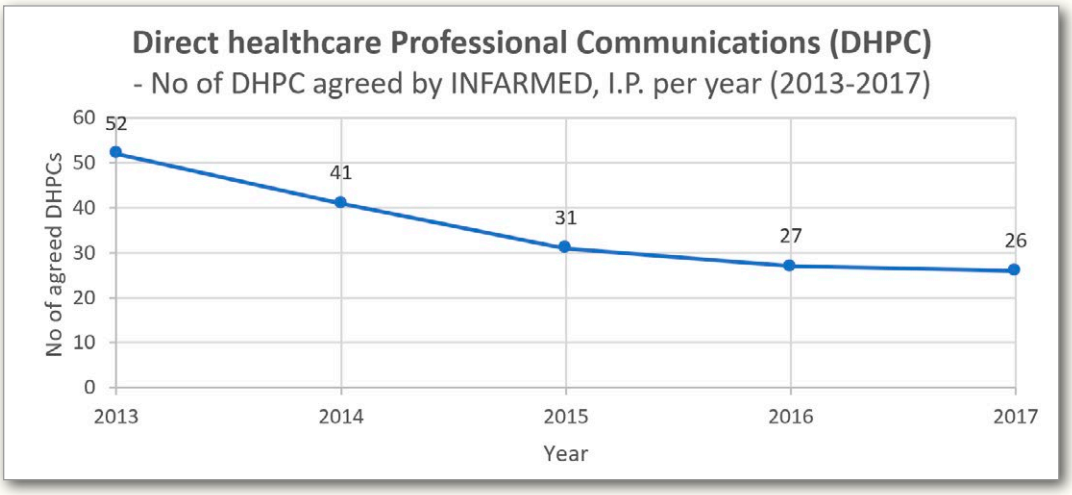
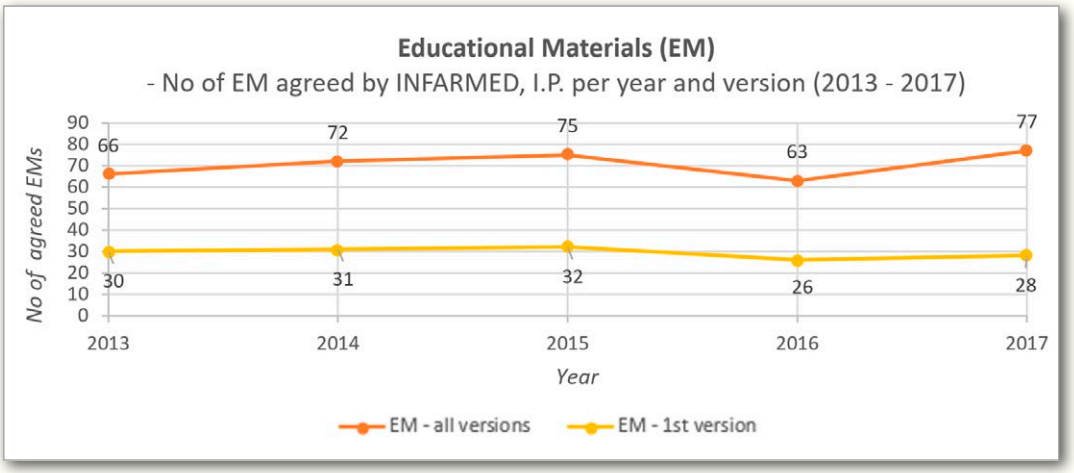
Educational Materials and Direct Healthcare Professional Communications: a review

Risk minimization measures (RMMs) are necessary for safe and effective use of medicines. Every medicinal product has routine RMMs associated, such as the Summary of the Product's Characteristics (SPC), the Patient Information Leaflet (PL), package labelling, the size or number of product units per package, etc. Exceptionally however, routine RMMs need to be complemented by **additional risk minimization measures (aRMMs),** of which **Educational Materials (EMs)** and Direct Healthcare Professional Communications (DHPCs) are two major examples. In Portugal, Marketing Authorization Holders are responsible for implementing aRMMs, once agreement is obtained from Infarmed.

The EMs and DHPCs agreed with Infarmed **between 2013 and 2017** were reviewed*. As the timeline graph below shows, a total of 177 DHPCs were validated in that period. Most (37%) involved **antineoplastic agents and immunomodulators**, followed by anti-infectious agents (10%) and hormones and medicines used in the treatment of endocrinological conditions (9%).



In the same period, 353 EMs were agreed upon (timeline graph below). Of these, 42% were first versions, i.e., new EMs. The remainder were updates of pre-existing EMs produced on account of developments in the knowledge of the safety profile of the corresponding medicines. **Antineoplastic and immunomodulator agents** were again the medicinal product classes most frequently involved (36%). Medicines for **central nervous system and blood** conditions came next (14% and 11%, respectively).



In the five years studied different trends were observed regarding submission of EMs and DHPCs to Infarmed. Whereas DHPCs decreased, EMs remained constant with over half of all submissions pertaining to updates of previously approved versions.

Sílvia Duarte, Ana Isabel Severiano, Márcia Silva, Ana Sofia Martins, Magda Pedro, Maria Fernanda Marques

** Poster presented at the "Innovation in Pharmacovigilance" symposium, Infarmed, Lisbon, 10-12-2018.*

Educational Materials published in the Infomed product information webpage

Click on the links.

INN Medicinal product	Target	Comunication Online publication date
Adalimumab Humira	**Patients**	Safety card
	Paediatric patients / caregivers	Safety card 1-03-2019
Adalimumab Hyrimoz	**Physicians:** rheumatology, dermatology, internal medicine, gastroenterology, ophthalmology, paediatrics	Guide
	Patients	Safety card 28-03-2019
Agomelatine Agomelatina TAD	**Physicians:** psychiatrics, neurology, internal medicine, general/family medicine	Guide
	Patients	Guide 12-03-2019
Axicabtagene ciloleucel Yescarta	**Healthcare professionals:** in multidisciplinary teams in qualified centres in charge of managing patients under treatment with this medicinal product	Handling and administration guide Serious adverse neurological reaction and cytokine release syndrome management guide
	Patients	Alert card 14-03-2019
Blinatumomab Blincyto	**Physicians:** haematology and paediatrics prescribers at centres treating ALL	Educational brochure
	Nurses: haematology departments in hospitals treating ALL, including paediatric hospitals	Educational brochure
	Pharmacists: in hospitals treating ALL, including paediatric hospitals	Educational brochure
	Patients and caregivers	Educational brochure
	Patients	Alert card 28-03-2019
Daptomycin Cubicin	**Physicians:** internal medicine, intensive care, surgery, infectious diseases, paediatrics, cardiology and dermatology – at hospitals where this medicinal product is used	Posology guide
	Healthcare professionals: in clinical labs at hospitals where this medicinal product is used	Determining sensitivity to Cubicin (daptomycin)
Eculizumab Soliris	**Physicians:** haematology	Guide for prescription in Nocturnal Paroxystic Haemoglobinuria (NPH)
	Physicians: neurology	Guide for prescription in generalized refractory Miasthenia Gravis (gMG)
	Physicians: nephrology	Guide for prescription in Atypical Haemolytic-Uraemic Syndrome (aHUS)
	Patients/Parents/Caregivers	Information brochure – NPH Information brochure – refractory gMG Information brochure aHUS 25-03-2019

Educational Materials published in the Infomed product information webpage

Click on the links.

INN Medicinal product	Target	Comunication Online publication date
Emtricitabine + Tenofovir disoproxil Emtricitabina + Tenofovir disoproxil Krka	**Physicians:** potential prescribers of this medicinal product as PrEP (in adults), namely specialists in infectious diseases and internal medicine	Educational brochure – pre-exposure prophylaxis (PrEP) Checklist
	At-risk adults	Educational brochure – pre-exposure prophylaxis (PrEP) Reminder card – pre-exposure prophylaxis (PrEP) 4-03-2019
Infliximab Fliximab	**Physicians:** rheumatology, dermatology, gastroenterology; paediatrics (gastroenterology) **Pharmacists:** pharmaceutical service directors	Safety information guide 18-03-2019
Infliximab Zessly	**Physicians:** potential prescribers - rheumatology, gastroenterology, dermatology, internal medicine (dealing with autoimmune diseases); paediatrics (gastroenterology) **Pharmacists:** pharmaceutical service directors **Nurses:** heads of services where this medicine is administered	Important safety information 28-03-2019
Macitentan Opsumit	**Physicians:** prescribers specialized in the treatment of pulmonary arterial hypertension and who do the hospital follow-up of patients on this medicine **Pharmacists:** at pharmaceutical services procuring this medicinal product	Prescription checklist Brochure for healthcare professionals: important safety information 13-03-2019
Medicinal products containing Hydroxyethylamide (HES) Tetraspan Venofundin Volulyte Voluven Fresenius	**Healthcare professionals:** who prescribe or administer products containing hydroxyethylamide	Brochure
	Heads of departments: where products containing hydroxyethylamide are used	Commitment letter 4-03-2019
Methylphenidate Metilfenidato ratiopharm	**Physicians:** psychiatrics, paediatrics and neurology	Prescriber guide Pre-prescription checklist In-treatment checklist Therapeutic monitoring table 28-03-2019
Naloxone Nyxoid	**Healthcare professionals:** integrated response centres, specialist teams and NGOs – co-ordinated by a physician/nurse in charge (Naloxone programme)	Administration training and support
	Patients	Information card Video 8-03-2019

Compiled by Magda Pedro

Communications to Healthcare Professionals published on the Infarmed website

Click on the links.

INN Medicinal product	Target	Comunication Online publication date
Belimumab Benlysta	**Physicians:** rheumatology, internal medicine, psychiatrics, nephrology, dermatology; directors of emergency services	Increased risk of serious psychiatric events (depression, suicidal ideation or behaviour, or self-inflicted harm) 27-03-2019
Deoxycholic acid Belkyra	**Physicians:** plastic surgery	Risk of necrosis at site of injection 14-03-2019
Dexamethasone Ozurdex	**Physicians:** ophthalmologists specialized in retina	Update on detection of silicone particles, availability of new, quality-issue-free batches and withdrawal of any units still remaining in the market 14-03-2019
Elvitegravir + Cobicistat + Emtricitabine + Tenofovir Stribild **Elvitegravir + Cobicistat + Emtricitabine + Tenofovir alafenamide** Genvoya	**Physicians:** infectious diseases and internal medicine specialists following up HIV-infected patients; paediatricians following up HIV-infected adolescents; hospital paediatrics and gynaecology/ obstetrics department directors **Nurses:** hospital nursing service directors at infectious diseases and internal medicine departments **Pharmacists:** hospital pharmacy service directors	Increased risk of HIV infection treatment failure and mother-child transmission due to lowered levels of exposure to elvitegravir and cobicistat during the second and third trimesters of pregnancy 26-03-2019
Rufinamide Inovelon – suspensão oral	**Physicians:** paediatrics and neurology **Pharmacists**	Incorrect figures printed on syringes provided with 40 mg/ml oral suspension vials 6-03-2019
Tofacitinib Xeljanz	**Physicians:** rheumatologists, internists and dermatologists who see rheumatoid arthritis and psoriatic arthritis patients; gastroenterologists	Increased risk of pulmonary embolism and mortality in patients with rheumatoid arthritis on 10 mg bid in a clinical trial 6-03-2019

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