boletim de FARMACO VIGILÂNCIA

VOLUME 24
NUMBER 3
MARCH 2020

Direct anticoagulants
no change to conditions of use

Quick Read
A study promoted by the European Medicines Agency (EMA) has concluded that no changes to the use of direct oral anticoagulant agents are necessary. The elderly (> 75 years) have a known increased risk of haemorrhage which on its own does not require any dose adjustments.

Direct oral anticoagulants (DOAC) act by selectively and reversibly inhibiting a coagulation factor, either factor IIa (dabigatran) or factor Xa (rivaroxaban, apixaban, edoxaban) with no direct effects on platelet aggregation. DOACs are indicated for the prevention of coagulation phenomena in various conditions, including nonvalvular atrial fibrillation (NVAF), and they are also used in the treatment of deep venous thrombosis (DVT), pulmonary embolism (PE), as well as in the prevention of recurrent DVP and PE in adults.

DOACs have become an alternative to treatment with classical anticoagulants, namely vitamin K antagonists (VKAs: essentially coumadin derivatives such as warfarin), whose action is limited by a slow start, a narrow therapeutic window, variable cytochrome P450 dependent metabolism, multiple interactions with food and drugs, and by a risk of haemorrhagic complications.

A **European study** promoted by EMA, based on "real world" data from six countries, looked at the **risk of serious haemorrhage** associated with the DOACs apixaban (Eliquis®), dabigatran (Pradaxa®) and rivaroxaban (Xarelto®) comparatively to VKAs in patients with NVFA. **Compliance in clinical practice** with the authorized information for those DOACs, particularly concerning therapeutic indications, contraindications, warnings and special precautions for use, and drug interactions, was also studied.

In general, the results confirm the patterns of haemorrhage of DOACs versus VKAs that are already listed in the Summaries of the Products' Characteristics. All three DOAC retain a favourable benefit-risk ratio for the authorized indications. Additionally, no robust evidence was found of lack of compliance to each product's authorized information.

The already previously known increased risk of haemorrhage in the elderly older than 75 years was also confirmed, however not in such a way that any dose adjustments would need to be recommended for this age group.

Finally, additional studies will be necessary to determine variations in risk level among different DOACs.

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Design and production: Letras & Sinais, Comunicação e Imagem, Lda.
ISSN: 0873-7118

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Communications to Healthcare Professionals published n the Infomed product information webpage

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INN Medicinal product	Target	Comunication Online publication date
Ulipristal Esmya	**Physicians:** gynaecologists and obstetricians, hepatologists/ gastroenterologists, medical dpt directors, Portuguese Society of Gynaecology (SPG), Portuguese Society of Reproduction Medicine (SPMR), Portuguese Society of Contraception (SPDC), Federation of the Portuguese Societies of Obstetrics and Gynaecology (FSPOG), Portuguese Society of Gastroenterology (SPG) **Pharmacists:** community and hospital **Wholesalers**	Not to be used while safety review on liver injury risk is ongoing 18-03-2020

Compiled by Patrícia Catalão

Educational Materials published on the Infomed product information webpage

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INN Medicinal product	Target	Comunication Online publication date
Adalimumab Idacio Imraldi Hulio Hyrimoz	**Patients**	Safety card 18-03-2020
Dienogest + Ethynilestradiol Serisima Diário	**Physicians:** gynaecologists and GPs/family doctors who conduct family planning clinics	Prescriber's checklist
	Patients	Information card 12-03-2020
Eculizumab Soliris		**Prescription guides for patients with:**
	Physicians: haematologists	Paroxysmal nocturnal haemoglobinuria (PNH)
	Physicians: nephrologists	Atypical hemolytic-uremic syndrome (aHUS)
	Physicians: neurologists	Generalized refractory myasthenia gravis (gMG) Neuromyelitis optica spectrum disorder (NMO)
	Patients	**Information brochures for patients with:** Generalized refractory myasthenia gravis (gMG) Neuromyelitis optica spectrum disorder (NMO) 26-03-2020
Etanercept Erelzi caneta pré-cheia 50 mg/1 ml Erelzi	**Healthcare professionals:** rheumatologists, dermatologists and internists, corresponding nurses, and hospital pharmacists (directors or pharmacists in charge)	Demonstration kit guide (pre-filled pen)
	Patients	Alert card (all presentations) 24-03-2020

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INN Medicinal product	Target	Comunication Online publication date
Fluocinolone acetonide Iluvien	**Physicians:** ophthalmologists	Administration guide Administration demonstration videoclip
	Patients	Safety information Safety information audio 19-03-2020
Lenalidomide Revlimid	**Physicians:** haematologists at healthcare units where prescription and dispensation of this product are available **Pharmacists:** pharmaceutical services at healthcare units where prescription and dispensation of this product are available	Safety information Advice checklist – women WITH childbearing potential Advice checklist – women WITHOUT childbearing potential Advice checklist – male patients Pregnancy report form ADR report form
	Patients	Booklet for women WITH childbearing potential Booklet for women WITHOUT childbearing potential Booklet for male patients 09-03-2020
Natalizumab Tysabri	**Physicians:** neurologists conducting a multiple sclerosis clinic	Safety information 13-03-2020
Pomalidomide Imnovid	**Physicians:** haematologists who treat patients with multiple myeloma **Pharmacists:** pharmaceutical services of units treating patients with multiple myeloma	Brochure for healthcare professionals Confirmation form – male patients Confirmation form – women WITH childbearing potential Confirmation form – women WITHOUT childbearing potential Pregnancy report form ADR report form
	Patients	Patient brochure – women WITH childbearing potential Patient brochure – women WITHOUT childbearing potential Patient brochure – male patients 09-03-2020

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INN Medicinal product	Target	Comunication Online publication date
Ravulizumab Ultomiris	**Physicians:** haematologists	Prescribing physician's guide Vaccination certificate
	Patients	Patient guide Alert card 24-03-2020
Tofacitinib Xeljanz	**Physicians:** rheumatologists, internists and dermatologists (therapeutic indications: rheumatoid arthritis and psoriatic arthritis); gastroenterologists (therapeutic indication: ulcerative colitis)	Prescribing physician's guide Checklist for starting treatment Checklist for maintenance treatment
	Patients	Alert card 12-03-2020
Treprostinilo Tresuvi	**Physicians:** cardiologists, pneumologists and surgeons	Information Training for healthcare professionals on catheter-related bloodstream infection risk Adverse event report form
	Patients	Information guide – use of a perfusion system Questionnaire 24-03-2020

Compiled by Patrícia Catalão

ADRs in the Literature
Medicinal herbs: drug interactions

Medicinal herbs contain pharmacologically active molecules with therapeutic potential. By the same token a potential for adverse reactions and drug interactions should be expected. Albeit incipient, evidence for both types of effects has been increasing.

The article by Izzo AA et al proposes an approach for the assessment of clinical efficacy, adverse reactions and herb-drug interactions based on systematic reviews and meta-analyses published in the last few years in Western countries. Various case study reports, case series and pharmacokinetic studies have underscored how medicinal herbs can interact with drugs in a clinically significant way. The Table below shows **examples of herb-drug interactions that are well documented in the literature** and which illustrate how every therapeutic product can have both benefits and risks.

Medicinal herb	Drug	Interaction
Danshen *Salvia milthiorriza* and Don quai *Angelica sinensis*	Warfarin	Increased anticoagulant effect
Evening primrose *Oenothera biennis*	Fluphenazine	Seizures
Garlic *Allium sativum*	Paracetamol Saquinavir	Pharmacokinetic changes Decreased serum concentration
Ginseng (American) *Panax quinquefolius*	Warfarin	Decreased anticoagulant effect
Goji *Lycium barbarum*	Warfarin	Increased anticoagulant effect
Green tea *Camellia sinensis*	Folic acid	Decreased serum concentration
Hibiscus *Hibiscus sabdariffa*	Cloroquine Paracetamol	Decreased serum concentration Pharmacokinetic changes
Milk thistle *Silybum marianum*	Metronidazole	Decreased serum concentration
St John's Wort *Hypericum perforatum*	Alprazolam, amitriptyline, bupropion, ciclosporin, digoxin, fenprocoumon, fexofenadine, gliclazide, imatinib, indinavir, irinotecan, methadone, midazolam, nevirapine, nifedipine, omeprazole, verapamil, warfarin, and zolpidem	Decreased serum concentration (in the case of ciclosporin, pharmacokinetic changes have been associated with episodes of transplant rejection)
	Oral contraceptives	Decreased efficacy and increased bleeding
	Paroxetine and venlafaxine	Serotoninergic syndrome
Peppermint *Mentha piperita*	Felodipine	Increased serum concentration

- ***Izzo AA et al. A Critical Approach to Evaluating Clinical Efficacy, Adverse Events and Drug Interactions of Herbal Remedies. Phytother Res (2016) 30: 691–700.***

Ziemann J et al took a step further to create a practical and flexible tool to assess the probability of interaction between drugs used in cancer therapy and medicinal herbs.

Based on a systematic literature review on interactions involving five common medicinal herbs (echinacea, ginseng, milk thistle, mistletoe and St John's wort), they used an expert panel consensus methodology to devise an algorithm whose results are presented in the form of a colour-coded matrix of risk categories (interaction probability levels) – these go from "interaction not expected" to "interaction likely expected". Categories corresponding to lack of data for a reliable estimate are also included.

The algorithm prioritizes clinical trial results over case study reports and in vitro trials. It reflects 529 sets of data obtained from 154 eligible studies out of 882 publications reviewed. In practical terms, this is an easy-to-use and constantly updatable pharmacological and clinical study evidence based tool for determining the risk of pharmacokinetic interactions between medicinal herbs and chemotherapeutic agents.

- ***Ziemann J et al. Herb-drug interactions: a novel algorithm-assisted information system for pharmacokinetic drug interactions with herbal supplements in cancer treatment. Eur J Clin Pharmacol. 2019 Sep;75(9):1237-1248.***

You can find in **this Boletim** a practical drug-drug interaction probability tool.