boletim de FARMACOVIGILÂNCIA

VOLUME 25
NUMBER 2
FEBRUARY 2021

Clarithromycin
risk of interaction with direct oral anticoagulants

Quick Read
In patients on a DOAC (apixaban, dabigatran, rivaroxaban), concomitant use of clarithromycin can be associated with and increased risk of bleeding.

Clarithromycin is a macrolide antibacterial agent used in the treatment of upper and lower respiratory tract, skin and soft tissue and dental infections, as well as in Helicobacter pylori eradication therapy.

The European Medicines Agency has concluded that there is at least a reasonable probability for an **interaction between clarithromycin and direct oral anticoagulants (DOACs)**. This has ensued from the latest Periodical Safety Report assessment of products containing clarithromycin which was finalised in January 2021. Data analysed included the Sarrazin MV et al. and the Garonzik S et al. studies on interaction between clarithromycin and apixaban and dabigatran, in addition to data relating to macrolide-rivaroxaban interaction, in both cases supported by a plausible mechanism: P-glycoprotein (P-gp) efflux transporter inhibition by clarithromycin. In addition to the already existing warning concerning warfarin, a new warning will be included in the Summaries of the Product's Characteristics (SmPCs) of clarithromycin-containing medicinal products.

Other risks were also assessed in the above safety report review. Further changes to the SmPCs of clarithromycin-containing medicinal products have resulted, namely:

- Contraindication in patients with **hypokalaemia** or with **hypomagnesaemia**, on account of a risk of QT interval prolongation.
- Contraindication concerning concomitant administration with the cholesterol-lowering agent **lomitapide** because of potential occurrence of a marked rise in liver transaminases.
- Use in **pregnancy** not recommended without careful consideration of the benefit-risk balance (possibly increased risk of miscarriage during the second and third trimesters; contradictory data regarding risk of congenital malformations).

Sílvia Duarte

INDEX CARD

Director: Fátima Canedo
Editor: Rui Pombal
Contributors: Adriana Gamboa, Ana Severiano, Ana Sofia Martins, Cristina Mousinho, Fátima Bragança, Fátima Hergy, Magda Pedro, Márcia Silva, Patrícia Catalão, 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
Design and production: Letras & Sinais, Comunicação e Imagem, Lda.
ISSN: 0873-7118

February highlights from the Pharmacovigilance Risk Assessment Committee (PRAC)

Velkury® (remdesivir):

- not associated with risk of acute renal injury

See here the start of the assessment of this suspected safety issue. The risk of acute kidney injury will continue to be carefully monitored within the scope of the safety reports that the marketing authorisation holder is to submit periodically.

- start of the assessment of a novel safety signal…

… following reports of cases of adverse cardiac events: sinus bradycardia, arrhythmia, hypotension and shock. A causal nexus is unclear at this time.

Strimvelis®: long-term follow-up on account of oncological risk

From the analysis of a single case of T lymphocyte leukaemia in a patient being treated with Strimvelis® in 2016 the need to send a Dear Healthcare Professional Communication was agreed on. This concerns the risk of genetic mutations associated with this gene therapy, which have a potential to cause cancer.

Strimvelis® (autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence) is indicated for the treatment of patients with severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID), for whom no suitable human leukocyte antigen (HLA)-matched related stem cell donor is available.

Venclyxto®: minimisation of the risk of tumour lysis syndrome

A communication to healthcare professionals is to be sent out to raise awareness of the risk of tumour lysis syndrome and to underscore the need for risk mitigation measures to be followed as per the Summary of the Product's Characteristics (SmPC).

Venclyxto® (venetoclax) is a medicine used for the treatment of adult patients with chronic lymphocytic leukaemia (CLL). CLL cells have great quantities of Bcl2 protein, to which venetoclax attaches thus blocking it and leading to cell death.

Zolgensma®: testing in order to minimise the risk of thrombotic microangiopathy

Thrombotic microangiopathy is a serious condition that causes thrombocytopenia, haemolytic anaemia and acute kidney injury. It has been decided that a communication to healthcare professionals needs to be sent out concerning this risk , including adequate ancillary means to be used to minimise it.

Zolgensma® (onasemnogene abeparvovec) is a gene therapy indicated for the treatment of spinal muscular atrophy.

Communications to Healthcare Professionals published in the Infomed product information webpage

Clique nas hiperligações para consultar

INN Medicinal product	Target	Communication? Online publication date
Ulipristal *Esmya, Ulipristal Accord*	**Physicians:** gynaecology and obstetrics, hepatology/gastroenterology, general/family medicine; clinical directors; Portuguese Societies of Gynaecology (SPG), of Reproduction Medicine (SPMR), of Contraception (SPDC), and of Gastroenterology (SPG), Federation of the Portuguese Societies of Obstetrics and Gynaecology (FSPOG)	Indications for uterine myomas restricted due to concerns with serious liver injury
	Pharmacists: community and hospital	20-02-2021

Compiled by Patrícia Catalão

ADRs in the Literature
Sulphonylureas and metformin not associated with significant haemorrhagic risk

Warfarin, a vitamin K antagonist, is a widely prescribed anticoagulant for the prevention and treatment of thromboembolic events and complications. Though rarely, haemorrhagic episodes can supervene with this type of therapy.

Metformin and sulphonylureas are very commonly used in the treatment of diabetes mellitus. They are often taken concomitantly with warfarin.

This study consisted of an analysis of a series of self-controlled cases containing "real life" health data from the US Medicaid system population. The authors looked at the simultaneous use of warfarin and oral antidiabetics (glimepiride, glipizide, gliburide, metformin) and concluded against a significant increase in the risk of serious bleeding.

These results reinforce previous epidemiological evidence supporting the view that the use of sulphonylureas or metformin does not have to be avoided in patients on anticoagulation therapy with warfarin.

• ***Nam YH et al. Sulfonylureas and Metformin Were Not Associated With an Increased Rate of Serious Bleeding in Warfarin Users: A Self-Controlled Case Series Study. Clin Pharmacol Ther. 2020 Nov;108(5):1010-1017***

Educational Materials published in the Infomed product information webpage
Click on the links

INN Medicinal product	Target	Materials? Online publication date
Mycophenolic acid *Ácido Micofenólico Accord, Myfortic*	**Physicians:** nephrology, urology, gastroenterology, cardiology, surgery, cardiothoracic surgery, general surgery, haematology, rheumatology, internal medicine, pneumology, neurology, obstetrics/gynaecology	Guide: teratogenicity risk
Mycophenolate mofetil *Cellcept, Micofenolato de Mofetil Accord, Micofenolato de Mofetil Aristo, Micofenolato de mofetil Generis, Mycophenolate Mofetil Teva, Myfenax*	**Pharmacists:** hospital **Patients**	Guide: risks for the unborn baby 19-02-2021
Valproic acid *Ácido Valpróico Generis, Ácido Valpróico Ratiopharm 300 mg, Ácido Valpróico Ratiopharm 500 mg Depakine, Depakine Chrono 300, Diplexil, Diplexil 150, Diplexil 300, Diplexil 500, Diplexil 1000, Depakine Chronosphere, Epixival, Valproato de sódio Altan* **Valproate semisodium** *Diplexil-R*	**Physicians:** neurology, psychiatry, general/family medicine, paediatrics – child psychiatry and neuropaediatrics **Patients**	Prescriber's guide Patient information guide 22-02-2021

Cont'd ▶

▶ *Cont'd*

INN Medicinal product	Target	Materials? Online publication date
Aflibercept *Eylea*	**Physicians:** ophthalmologist prescribers **Patients**	**Recommendations for the physician** **Intravitreal injection procedure - videoclip** **- Guides for patients with loss of vision due to:** **Myopic choroidal neovascularisation (myopic CNV)** **Diabetic macular oedema (DME)** **Macular oedema secondary to branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO)** **- Guides for patients with:** **Neovascular age-related macular degeneration (wet AMD)** 04-02-2021
Apixaban *Eliquis*	**Physicians:** cardiology, neurology, internal medicine, general/family medicine, haematology/immune-haemotherapy, anaesthesiology, orthopaedic surgery, vascular surgery, gastroenterology; clinical directors **Pharmacists:** hospital pharmaceutical service directors	**Prescriber's guide** 27-02-2021
Belantamab mafodotin *Blenrep*	**Physicians:** ophthalmology **Physicians:** haematology **Patients**	**Guide to corneal adverse reactions** **Guide to corneal adverse reactions** **Ophthalmological screen sheet** **Guide to undesirable corneal reactions** **Patient card** **Eye drop card for pharmacies** 27-02-2021
Blinatumomab *Blincyto*	**Physicians:** haematology and paediatrics prescribers at centres treating ALL patients	**Educational brochure** 11-02-2021
Brolucizumab *Beovu*	**Patients**	**Guide** 11-02-2021
Bromelain *Nexobrid*	**Physicians:** plastic surgery, anaesthesiology and intensive care medicine **Nurses**	**Safety information for burn unit healthcare professionals** 25-02-2021

Cont´d ▶

▶ *Cont'd*

INN Medicinal product	Target	Materials? Online publication date
Delamanid *Deltyba*	**Healthcare professionals:** in charge of prescribing, dispensing and administering this medicinal product	Guide
	Patients	Guide 25-02-2021
Fentanyl *PecFent*	**Physicians:** oncology, pain specialists, palliative care specialists **Pharmacists:** community and hospital	Healthcare professional guide
	Patients	Patient and caregiver guide 25-02-2021
Thalidomide *Thalidomide Celgene*	**Physicians:** haematology	Information: prescribing and dispensing **- Treatment start forms for:** Women of childbearing potential Women without childbearing potential Males Adverse event report form **-Pregnancy exposure forms:** History and start of pregnancy Pregnancy outcome **Information for:** Women of childbearing potential Women without childbearing potential Males
	Patients	25-02-2021

Compiled by Patrícia Catalão