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Methotrexate
potentially fatal medication errors

Quick Read
Measures to prevent potentially fatal medication overdosing have been reinforced, namely concerning daily instead of weekly administration in the treatment of autoimmune disorders.

Methotrexate is approved in Portugal for two distinct types of indications each with its own specific regime:
- *malignant neoplasms – variable frequency of administration which may be qd;*
- *autoimmune conditions, including rheumatoid arthritis and psoriasis – once weekly administration.*

In spite of measures previously adopted to prevent medication errors to do with mixing up the two different administration regimes for each group of clinical indications, serious and occasionally fatal cases have still since been reported in patients with autoimmune diseases who received a daily instead of a weekly posology regime.

A European safety review has concluded that those errors can occur at all stages of the therapeutic cycle from prescription to administration.

New measures have therefore been introduced to prevent dosing errors, including **prominent warnings** on both the outside and inside packaging, as well as updates to the Summary of the Product Characteristics and the Information Leaflet. **Educational materials addressing healthcare professionals** have been agreed on for oral formulations and a patient card will be inserted in the packaging.

Methotrexate should only be **prescribed by physicians with experience** in using this medication. Healthcare professionals who prescribe or dispense methotrexate for the treatment of autoimmune conditions should strive to ensure that the patient/caregiver:

- receives clear and complete instructions on dosing for the weekly therapeutic regime;
- understands, at each prescription/dispensation renewal, that the medicinal product should be taken once a week;
- sets a fixed day of the week to take methotrexate;
- knows the signs of overdosing and that they should prompt immediate seeking of medical advice.

As for the **Alert Card** in the packaging, healthcare professionals should make sure that the patient:

- knows about the card and jots down the day of the week they should take the medicine;
- has it on them at all times and knows they should show it to any healthcare professionals who may not be familiar with this therapy.

Ana Isabel Severiano

INDEX CARD

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Educational Materials published in the Infomed product information webpage

Click on the links.

INN Medicinal product	Target	Materials? Online publication date
Brivudine Bridic	**Physicians:** general/family medicine, internal medicine, oncology, dermatology	Checklist 12-05-2020
Dabigatran Pradaxa	**Physicians:** orthopaedics	Prescription guide for use in primary prevention of venous thromboembolic events in adults submitted to elective total hip or knee arthroplasty
	Physicians: general/family medicine, internal medicine, cardiology, neurology, haematology, clinical pathology, gastroenterology, immunohaemotherapy, anaesthesiology, vascular surgery, neurosurgery, general surgery	Prescription guide for use in cardiovascular indications (NVAF, DVT and PTE) 05-05-2020
Emtricitabine + Tenofovir Emtricitabina + Tenofovir Farmoz	**Physicians:** potential PrEP prescribers, namely infectious diseases specialists, internists and paediatricians (following up HIV-infected adolescents)	Educational brochure (PrEP) Checklist (PrEP)
	Patients (at-risk individuals)	Educational brochure (PrEP) PrEP reminder card 05-05-2020
Emtricitabine + Tenofovir Emtricitabina + Tenofovir Farmoz Tenofovir Farmoz Tenofovir Aurovitas	**Physicians:** infectious diseases, internal medicine, gastroenterology, and paediatrics	Recommendations for use in the treatment of adolescents with chronic hepatitis B and/or HIV-1 infection 05-05-2020
Trastuzumab Kadcyla	**Physicians:** oncologists, radiotherapists, general surgeons, gynaecologists, and internists in charge of senology clinics and experienced in anti-HER2 therapy **Nurses:** hospital **Pharmacists:** hospital	Healthcare professional guide 12-05-2020

Compiled by Patrícia Catalão

Concomitant administration of sofosbuvir and amiodarone: cardiac monitoring of every patient

Quick Read
During administration of amiodarone and in the first months after its discontinuation, every patient and not only those with risk factors, should be followed with cardiac monitoring for at least the first two weeks of treatment with sofosbuvir.

The PRAC at EMA has recommended that, on account of risk of severe bradycardia and heart block, all patients on hepatitis C treatment with products containing sofosbuvir (Epclusa®, Harvoni®, Sovaldi®, Vosevi®) simultaneously with the antiarrhythmic amiodarone should be monitored in an adequate clinical environment during the first 48 hours of concomitant therapy. Following that and for at least the first two weeks of treatment, daily ambulatory monitoring should be undertaken.

Because of amiodarone's long half-life, patients who have stopped taking amiodarone within the preceding few months and who are starting treatment with products containing sofosbuvir should also undergo cardiac monitoring.

Patients should be warned about the symptoms of bradycardia and heart block and should be advised to seek urgent medical help in case they supervene.

These recommendations have resulted from a recent European safety review of cases of bradyarrhythmia. Although this type of risk has been known for years and **risk minimization measures had already been implemented**, cases of bradyarrhythmia were still being reported. EMA has therefore considered that warnings in the SmPCs and PILs of both amiodarone and the above medicinal products for hepatitis C should be reinforced.

Ana Sofia Martins

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

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

ADRs in the literature
Safety of renin-angiotensin-aldosterone system inhibitors in patients with COVID-19

This Spanish case population study published in The Lancet has sought to address existing questions on the possibility of renin-angiotensin-aldosterone system (RAAS) inhibitors predisposing to more severe forms of COVID-19.

Data were collected from over 1,100 cases of adult patients admitted to seven hospitals in Madrid with PCR-confirmed COVID-19 in March 2020. For each case, ten paired controls were randomized from the Spanish Primary Care database. In spite of age and gender pairing, cases had a higher proportion of pre-existing cardiovascular disease and risk factors.

Compared to users of other antihypertensives, RAAS inhibitor users had an odds ratio of COVID-19 needing hospital admittance of 0.94. No increase in risk was seen either with angiotensin converting enzyme inhibitors or with angiotensin receptor antagonists. On the contrary, diabetic patients on RAAS inhibitors were associated with a decreased risk of need for hospitalization for COVID-19.

The authors conclude that RAAS inhibitors should not be discontinued in patients with COVID-19, since they are not expected to increase the risk of admission to intensive care units or death, nor of need for hospital admittance in general.

- ***Abajo F J et al. Use of renin–angiotensin–aldosterone system inhibitors and risk of COVID-19 requiring admission to hospital: a case-population study. Lancet. 2020;395(10238):1705-1714.***

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

INN Medicinal product	Target	Materials? Online publication date
Brivudine Bridic	**Physicians:** general/family medicine, internal medicine, oncology, and dermatology **Pharmacists:** community	Potentially fatal toxicity of fluoropyrimidines when given close to or at the same time as brivudine, or when used in the 4 weeks following discontinuation of brivudine 12-05-2020

Compiled by Patrícia Catalão