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Methotrexate
risk of pulmonary alveolar haemorrhage

Quick Read
Pulmonary alveolar haemorrhage has been reported in association with methotrexate for rheumatological and other related indications. Its incidence is unknown.

Methotrexate is an antineoplastic, immunomodulator agent that acts as a folic acid antagonist, thereby interfering with DNA synthesis and repair and with cell replication. It is authorized in the EU for two groups of indications with different administration regimes: a) Oncological therapy, including choriocarcinoma and blood neoplasms such as acute lymphoblastic leukaemia and non-Hodgkin lymphoma, with daily treatment, and b) Treatment of autoimmune diseases, such as rheumatoid arthritis and psoriasis, usually in their severe and recalcitrant forms requiring immunosuppressive therapy, usually with weekly therapy schedules.

Pulmonary toxicity is a well-known risk associated with this active ingredient. However, pulmonary alveolar haemorrhage, which usually requires immediate treatment, is not described in the information of products containing methotrexate.

Seventeen post-marketing cases with methotrexate have been reported, including 5 from the literature. Eleven cases were co-reported with interstitial pulmonary disease.

Taking into account the available information from the European database Eudravigilance and from the literature, the PRAC at EMA is recommending that the information for methotrexate-containing products be updated for their various indications. The following will be included in the Warnings and Special Precautions for Use (4.4) section of the SmPCs:

> In addition, pulmonary alveolar haemorrhage has been reported with methotrexate used in rheumatologic and related indications. This event may also be associated with vasculitis and other comorbidities. Prompt investigations should be considered when pulmonary alveolar haemorrhage is suspected to confirm the diagnosis.

The reported cases show sufficiently evidence only for the **medicines whose therapeutic indications are not strictly oncological**. Section 4.8 Contraindications in their SmPCs will include the undesirable effect pulmonary alveolar haemorrhage with frequency unknown.

Elsa de Fátima Costa

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Levetiracetam
conditions for safe use in pregnancy

Quick Read

Levetiracetam given during pregnancy as monotherapy does not seem to be associated either with fetal teratogenicity or with neurodevelopmental disorders in children exposed in utero. These risks cannot however be completely excluded. Use of levetiracetam during pregnancy needs to be adequately pondered and women informed and advised.

Levetiracetam, an antiepileptic agent whose mechanism of action is still not completely understood, is indicated as monotherapy for partial crises with or without secondary generalization, in adults and adolescents from 16 years of age with a de novo diagnosis of epilepsy, as well as adjuvant treatment for other forms of epilepsy in childhood and adolescence.

As agreed with the European Medicines Agency (EMA), the information for levetiracetam (Keppra®) was recently reviewed. A cumulative review of the cases of pregnant women exposed to monotherapy (over 1,800, including more than 1,500 exposures in the first trimester) did not suggest an increased risk of major congenital malformations. Nor do available epidemiological studies in around 100 children exposed in utero suggest an increase in neurodevelopmental disorders or delays.

No evidence has therefore been found of a safety problem in terms of **teratogenicity** or **neurodevelopmental toxicity** associated with levetiracetam **monotherapy**. However, available data were not considered sufficient to exclude those risks.

Treatment with levetiracetam should always be **reviewed by a specialist** whenever a patient with epilepsy is planning to become pregnant, and known risks should be reviewed. This medicine may be used during pregnancy provided that, following in-depth assessment, it is deemed clinically necessary. At the same time the following **recommendations** should be borne in mind:

- Use the **lowest effective dose**;
- Whenever possible, prefer **monotherapy** (treatment with multiple antiepileptic agents may be associated with a higher risk of congenital malformations than monotherapy);
- Ensure **adequate clinical follow-up**, since physiological changes during pregnancy can decrease the dose/plasma concentration ratio of levetiracetam, especially in the third trimester.

The SmPC and PL of Keppra® (levetiracetam) will be updated accordingly.

Ana Severiano

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

Educational Materials published in the Infomed product information webpage

Click on the links.

INN Medicinal product	Target	Materials? Online publication date
Adalimumab Humira	**Patients /Caregivers**	Administration guide for paediatric patients 01-06-2018
Alemtuzumab Lemtrada	**Physicians:** neurologists	Guide Prescriber's checklist
	Patients	Alert Card Guide 22-06-2018
Bupropion + Naltrexone Mysimba	**Physicians:** general/family physicians, endocrinologists, general surgeons and psychiatrists.	Prescriber's checklist 25-06-2018
Cholic acid Kolbam	**Physicians:** hepatologists and paediatricians	Educational Material 02-07-2018
Dabigatran etexilate Pradaxa, 110 mg e 150 mg	**Physicians:** general/family medicine, cardiology, internal medicine, neurology, haematology, clinical pathology, gastroenterology, immune-haemotherapy, anaesthesiology, vascular surgery, neurosurgery and general surgery.	Prescription guide for cardiovascular indications (NVAF, DVT and PET)
Pradaxa, 75 mg e 110 mg	**Physicians:** orthopaedic surgery	Prescription guide for indication in primary prevention of venous thromboembolism in adult patients submitted to total elective hip or knee arthroplasty 10-07-2018
Dronedarone Multaq	**Physicians**	Prescriber's guide 04-07-2018
Efavirenz + emtricitabine + tenofovir disoproxil Efavirenz + emtricitabina + tenofovir Mylan **Emtricitabine + tenofovir disoproxil** Emtricitabina + tenofovir Mylan **Tenofovir disoproxil** Tenofovir Mylan	**Physicians:** who follow up patients with HIV and HBV infections (infectious diseases, internal medicine, gastroenterology and paediatrics specialists)	Recommendations on renal control and dose adjustment in adult patients taking medicinal products containing tenofovir disoproxil 01-06-2018

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	At-risk individuals	Educational brochure on pre-exposure Reminder card on pre-exposure 07-06-2018
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	Patients and/or Caregivers	Guide 04-07-2018
Ipilimumab Yervoy	**Healthcare professionals:** dermatology and oncology departments, day care hospitals and pharmaceutical services in hospitals where Yervoy prescription or use can be expected.	Prescription guide
	Patients	Information guide Alert card 02-07-2018
Levonogestrel Jaydess Kyleena	**Physicians:** : gynaecologists, obstetricians and general/family physicians who conduct family planning clinics.	Differences between Jaydess, Kyleena and other intrauterine release devices 04-06-2018
Nilotinib Tasigna	**Physicians:** specialists in oncology, paediatric onco-haematology. **Pharmacists:** directors of hospital pharmaceutical services.	Information brochure 04-06-2018
	Patients	Brochure on how to deal with your medication 01-06-2018
Romiplostim Nplate	**Physicians:** prescribers	Dose calculator
	Healthcare professionals: prescribing physicians and other healthcare professionals in charge of reconstitution and administration.	Self-administration checklist Selection and training of adult patients for administration at home
	Patients: selected for self-administration.	Self-administration diary for adult patients Step-by-step guide for preparation and administration at home Quick guide Preparation surface 07-06-2018

Compiled by Fernanda Marques and Magda Pedro

ADRs in the literature
Technical review through contact with reporting person improves case informativeness

For ADR reports to be adequately assessed it is often necessary to obtain additional data on the cases reported. The authors of this retrospective study encompassing four years of consumer reports received by a French pharmacovigilance centre assessed the informativeness of ADR reports before and after review by a pharmacovigilance assessor.

The number of key information pieces increased after review. For example, data on the time gap between beginning of exposure to the drug and the beginning of the ADR, which was initially available in only 51% of reports, became known in 83% of cases after review. Patient medical history and concomitant medication were not initially available in 3 out of 4 reports; following review they were missing in only 30% of cases.

In general, **contacting the reporting person increased report informativeness in over 90% of cases**. Pre-reporting patient/reporting person education and technical interventions to obtain further data are both strategies the authors deem able of raising the informativeness of ADR reports.

Kheloufi F et al. Informativeness of patient initial reports of adverse drug reactions. Can it be improved by a pharmacovigilance centre?. Eur J Clin Pharmacol. 2017; 73(8),1009-18.

Communications to Healthcare Professionals published on the Infarmed website
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Nusinersen Spinraza	**Physicians:** neurologists and neuropaediatricians.	Reported cases of communicating hydrocephalus not related with meningitis or haemorrhage in patients with spinal muscular atrophy 30-07-2018
Pembrolizumab Keytruda	**Physicians:** oncologists and urologists. **Pharmacists:** directors of hospital pharmaceutical services.	Restriction of indication for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma deemed not eligible for chemotherapy with cisplatin 09-07-2018
Ulipristal Esmya	**Physicians:** GYN/OBS, hepatology/gastroenterology, general practice; Portuguese Societies of Gynaecology (SPG), Reproductive Medicine (SPMR), Contraception (SPDC), Gastroenterology (SPG); Federation of Portuguese Societies of Obstetrics and Gynaecology (FSPOG); Clinical Directors. **Pharmacists:** hospital and community	New contraindication, monitoring requirements and indication restriction 30-07-2018

Compiled by Fernanda Marques