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Gadolinium-containing agents
restrictions on use

Quick Read

Due to a risk of retention of gadolinium in tissues, namely in the brain, imaging contrast agents containing gadobenic acid (except for liver imaging), gadodiamide, gadopentetic acid and gadoversetamide, have been suspended. Other agents may continue to be used in restricted conditions (see below).

Gadolinium-containing contrast agents (GCCAs) are paramagnetic gadolinium (III) compounds with various types of organic chelants used to improve organ and tissue image quality in magnetic resonance and magnetic resonance angiography studies. GCCAs can be classified according to their structure – linear (gadodiamide, gadopentetic acid, gadobenic acid, gadoxetic acid, gadoversetamide) or macrocyclic (gadoteridol, gadobutrol, gadoteric acid) –, and according to the global charge of the final compound (ionic or non-ionic).

These agents can be administered before or during an MRI exam for contrast enhancement. After administration they are mostly eliminated by the kidneys. Studies have revealed however, that gadolinium may be retained in certain tissues and organs, including liver, kidney, muscle, skin and bone. There is more recent evidence that these contrast media can also be retained in brain tissue.

EMA has undertaken a safety review to assess the risk of deposition of gadolinium in brain tissue after use of contrast agents containing this substance. The risk was confirmed and greater retention in the brain of gadolinium from linear-structure than from macrocyclic GCCAs was observed. No evidence of harm was found in patients, nor of adverse neurological effects, such as cognitive or movement disorders. Nevertheless, **long-term risks are not known**. The European Commission has therefore taken the following decisions:

- The benefit-risk balance of intravenous medicinal products containing **gadobenic acid** (in all indications except liver imaging), **gadodiamide, gadopentetic acid** and **gadoversetamide** is no longer favourable; these products are therefore **suspended**.
- The **risk-benefit balance remains favourable** for the following agents when used with restrictions in the lowest necessary dose for diagnosis and only when essential diagnostic information cannot be obtained by non-enhanced MRI (without the use of contrast agents):
  - Macrocyclic agents **gadoteridol, gadobutrol** and **gadoteric acid**: since these are more stable and less likely to release gadolinium;
  - **Gadoxetic acid** and **gadobenic acid** (also designated as **dimeglumine gadobenate** on Infarmed's Infomed medicinal product search engine): these will still be available exclusively for **magnetic resonance imaging of the liver**, since they are absorbed by this organ and remain a significant diagnostic tool;
  - Linear agent **gadopentetic acid**: will remain available for **intra-articular** administration only (this indication does not apply to Portugal) for bone joint MRI, since the necessary concentration is very low.

The SmPCs and PILs are being updated accordingly. Additionally, the MA holders have sent a out a **DHCP letter**. For further information (in Portuguese), an **Information Circular** can be consulted at Infarmed's website. The **documentation regarding this referral** (assessment) is available on the EMA website.

Magda Pedro

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Assessment of the handling of the human papillomavirus vaccines referral: a worked example of the role of the European Ombudsman

Quick Read

The European Ombudsman issued in October last a decision on the handling by the European Medicines Agency (EMA) of a referral (assessment) concerning human papillomavirus vaccines. The conclusion was that there was no mishandling or conflict of interests.

The European Ombudsman is not a scientific body. For this reason, it does not look into the scientific assessments made by organizations. It does however assess whether the latter have in place background mechanisms to ensure that scientific assessments are complete and independent. It also makes sure that those procedures are adequately applied.

Human papillomavirus vaccines are administered for the prevention of diseases associated with the more common viral serotypes, including cervical and anal cancer.

The safety of human papillomavirus vaccines was reviewed through a referral (assessment) handled by EMA to assess the potential occurrence of two conditions which, albeit rare, have been reported after vaccination – complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS). All the available data were assessed, including those from consultation with a group of experts and with patient groups. It was concluded that there is no evidence supporting a causal relation, and there is no reason to change the way those vaccines are given, i.e. their benefits still outweigh their risks. The European Commission adopted the recommendations from this assessment in January 2016.

A group of complainants who disagreed with EMA's scientific assessment appealed to the European Ombudsman with concerns regarding how the referral (assessment) procedure was handled, its transparency, openness and impartiality. Following an inquiry, the Ombudsman found no issues that could have negatively affected the proceedings and the referral's conclusions. The importance of ensuring the trust of citizens in institutions such as EMA was however underscored, and the following suggestions made:

- Proactive publication of as much information as possible regarding EMA committees' scientific work;
- Increased availability of information on relevant documentation held by the agency to make it easier for citizens to access it.

EMA agreed to review its expert confidentiality requirements so that they may publicly discuss the details of the scientific debate once the latter has been concluded.

For more information, the **European Ombudsman's decision can be looked up here**. **The documentation on this referral can be found here**.

Ana Severiano

Communications to Healthcare Professionals published on the Infarmed website

Click on the links.

INN Medicinal product	Target	Comunication Online publication date
Ulipristal Esmya	**Physicians:** OB/GYN, hepatologists and gastroenterologists, general practitioners. **Healthcare professionals' organizations:** Portuguese Society of Gastroenterology, Portuguese Society of Reproductive Medicine and Federation of Portuguese Societies of Obstetrics and Gynaecology.	Restrictions for use, warnings on serious liver injury and recommendations for liver monitoring. 15-02-2018
Obeticholic acid Ocaliva	**Physicians:** all prescribers in centres specializing in the treatment of patients with primary billiary cholangitis (PBC), including hospital doctors in training and every medical doctor treating patients with PBC in early access / compassionate use programmes. **Pharmacists:** hospital pharmacists (including pharmacists in training) and all the directors of pharmaceutical services in hospitals with units treating PBC.	Clarification of recommendations regarding differences in posology in patients with primary billiary cholangitis (PBC) with moderate to serious liver impairment. 12-02-2018

Compiled by José Sequeira

Portal **RAM**

Notificação de Reações Adversas a Medicamentos

Report an adverse drug reaction here.

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Educational Materials published in the Infomed product information webpage

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INN Medicinal product	Target	Materials Online publication date
Abacavir Abacavir Sandoz **Abacavir + Lamivudine** Abacavir + Lamivudina Sandoz	**Physicians:** hospital infectious diseases and internal medicine department directors. **Pharmacists:** hospital pharmaceutical service directors.	Educational material on serious hypersensitivity reactions 09-02-2018
Emtricitabine + Tenofovir Emtricitabina + Tenofovir Sandoz	**Physicians:** internists and infectious diseases specialists	Safety information on pre-exposure prophylaxis (PrEP) Checklist for the prescribing physician (PrEP)
	Persons at risk	Reminder card (PrEP) Safety information on reduction of the risk of acquiring HIV infection (PrEP) 09-02-2018
Emtricitabine + Tenofovir Emtricitabina + Tenofovir Sandoz **Efavirenz + Emtricitabine + Tenofovir** Padviram	**Physicians:** internists and infectious diseases specialists	Recommendations on renal monitoring and dose adjustment in adult patients with HIV-1 infection 05-02-2018

Compiled by José Sequeira

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