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EMA's final opinion confirms restrictions on use of linear gadolinium agents in body scans

Recommendations conclude EMA's scientific review of gadolinium deposition in brain and other tissues

On 20 July 2017, the European Medicines Agency (EMA) concluded its review of gadolinium contrast agents, confirming recommendations to restrict the use of some linear gadolinium agents used in MRI body scans and to suspend the authorisations of others.

The recommendations – confirmed by EMA's Committee for Medicinal Products for Human Use (CHMP) – followed a review that found that gadolinium deposition occurs in brain tissues following use of gadolinium contrast agents.

There is currently no evidence that gadolinium deposition in the brain has caused any harm to patients; however EMA has recommended restrictions and suspensions for some intravenous linear agents in order to prevent any risks that could potentially be associated with gadolinium brain deposition.

The intravenous linear agents gadoxetic acid and gadobenic acid can continue to be used for liver scans because they are taken up in the liver and meet an important diagnostic need. In addition, gadopentetic acid given intra-articularly (into the joint) can continue to be used for joint scans because the dose of gadolinium used for joint injections is very low.

All other intravenous linear products (gadodiamide, gadopentetic acid and gadoversetamide) should be suspended in the EU.

Another class of gadolinium agents known as macrocyclic agents (gadobutrol, gadoteric acid and gadoteridol) are more stable and have a lower propensity to release gadolinium than linear agents. These products can continue to be used in their current indications but in the lowest doses that enhance images sufficiently and only when unenhanced body scans are not suitable.

The suspensions or restrictions on linear agents can be lifted if the companies concerned provide evidence of new benefits in an identified patient group that outweigh the risk of brain deposition or if the companies can modify their products so they do not release gadolinium significantly or cause its retention in tissues.

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EMA's scientific review of gadolinium deposition in brain and other tissues is now concluded. The final recommendations have been sent to the European Commission, which issued a final legally binding decision applicable in all EU Member States.

Product	Type (formulation)	Recommendation
Artirem / Dotarem (*gadoteric acid*)	macrocyclic (i.v.)	maintain
Artirem / Dotarem (*gadoteric acid*)	macrocyclic (intra-articular)	maintain
Gadovist (*gadobutrol*)	macrocyclic (i.v.)	maintain
Magnevist (*gadopentetic acid*)	linear (intra-articular)	maintain
Magnevist (*gadopentetic acid*)	linear (i.v.)	suspend
Multihance (*gadobenic acid*)	linear (i.v.)	restrict use to liver scans
Omniscan (*gadodiamide*)	linear (i.v.)	suspend
Optimark (*gadoversetamide*)	linear (i.v.)	suspend
Primovist (*gadoxetic acid*)	linear (i.v.)	maintain
Prohance (*gadoteridol*)	macrocyclic (i.v.)	maintain

Information for patients

- Gadolinium contrast agents are given to patients during body scans to help obtain a clear image of the inside of the body.
- It is known that small amounts of gadolinium may remain in the brain after a scan with these agents, although there is currently no evidence that these small amounts cause any harm.
- As a precaution, doctors will stop using some contrast agents given into the vein while some others will only be used when other agents are not suitable (e.g. for liver scans).
- Gadolinium contrast agents are essential for diagnosing a wide range of life-threatening and debilitating diseases.
- If you need a scan with a gadolinium contrast agent to help in your treatment, your doctor will use the lowest dose required for a clear image.
- If you have any questions about your scan, speak to your doctor.

Information for healthcare professionals

- Gadolinium deposition in the brain has been confirmed by mass spectrometry and increases in signal intensity in brain tissue.
- Data on stability, as well as *in vitro* and non-clinical studies, show that linear gadolinium agents release gadolinium from the ligand molecules to a greater extent than macrocyclic agents.
- No adverse neurological effects, such as cognitive or movement disorders, have been attributed to gadolinium deposition in the brain with any gadolinium agents.

- The marketing authorisations for the intravenous linear agents gadodiamide and gadoversetamide, as well as the intravenous formulation of the linear agent gadopentetic acid, are now suspended in the EU.
- Two intravenous linear agents – gadoxetic acid and gadobenic acid – remain available as these agents undergo hepatic uptake, and can be used for imaging poorly vascularised hepatic lesions, especially in delayed phase imaging, that cannot be adequately studied with other agents.
- Intra-articular formulations of the linear agent gadopentetic acid will continue to be available because the dose of gadolinium that is required for these scans is very low.
- All macrocyclic agents reviewed – gadobutrol, gadoteric acid and gadoteridol – also remain available.
- Healthcare professionals should use gadolinium contrast agents only when essential diagnostic information cannot be obtained with unenhanced scans.
- Healthcare professionals should always use the lowest dose that provides sufficient enhancement for diagnosis.
- The product information for gadolinium contrast agents remaining on the EU market is being updated accordingly.
- Healthcare professionals in the EU will be sent a letter with information about EMA's review of gadolinium contrast agents.

More about the medicines

Gadolinium contrast agents are used as contrast enhancers to improve image quality with magnetic resonance scans. These body scans rely on the magnetic fields produced by water molecules in the body. Once injected, gadolinium interacts with the water molecules. As a result of this interaction, the water molecules give a stronger signal, helping to obtain a brighter image.

This review covers agents containing the following active substances: gadobenic acid, gadobutrol, gadodiamide, gadopentetic acid, gadoteric acid, gadoteridol, gadoversetamide and gadoxetic acid.

Most gadolinium-containing contrast agents have been authorised nationally in the EU. OptiMARK (gadoversetamide) is the only gadolinium contrast agent that was authorised centrally via EMA in the EU.

More about the procedure

The review of gadolinium contrast agents was initiated on 17 March 2016 at the request of the European Commission, under Article 31 of Directive 2001/83/EC.

The review was first carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which made a set of recommendations in March 2017.

Following a request from companies concerned, the PRAC re-examined its initial recommendation. The PRAC's final recommendations were sent to the Committee for Medicinal Products for Human Use

(CHMP), responsible for questions concerning medicines for human use, which adopted the Agency's final opinion.

The final stage of the review procedure was the adoption by the European Commission of a legally binding decision applicable in all EU Member States. Commission decision date: 23/11/2017.