Restrictions on use of linear gadolinium agents in body scans confirmed

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Information on gadolinium agents

- Gadolinium contrast agents are used as contrast enhancers to improve image quality with magnetic resonance imaging (MRI) scans.
- The review covered following active substances classed as **linear products** (gadopentetic acid, gadobenic acid, gadodiamide, gadoversetamide, gadoxetic acid) and **macrocyclic agents** (gadobutrol, gadoteric acid and gadoteridol).
- Most gadolinium-containing contrast agents have been authorised nationally in the EU with the exception of OptiMARK (gadoversetamide) which is the only gadolinium contrast agent that is centrally authorised.

The linear gadolinium contrast agents authorised in Malta are:

Active Ingredients	Product Name	Pharmaceutical Form	Classif-cation	Authorisation Number	MAH/license holder
Gadodiamide	Omniscan	Solution for injection	POM	MA023/00101	GE Healthcare AS
Gadopentate dimeglumine	Magnevist	Solution for injection	POM	MA185/01001	Bayer PLC

Information on EMA's scientific review of gadolinium deposition in brain and other tissues

The European Medicines Agency (EMA) has concluded its scientific review of gadolinium deposition in brain and other tissues. The recommendation to restrict the use of some linear gadolinium agents used in MRI body scans and suspend the authorisations of others has been confirmed.

- There is currently no evidence that gadolinium deposition in the brain has caused any harm to patients but EMA has recommended restrictions 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. 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.

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- 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.

The review of gadolinium contrast agents was initiated on 17 March 2016 (refer to P10/2016) at the request of the European Commission and involved a re-examined of initial recommendation. The Pharmacovigilance Risk Assessment Committee (PRAC) final recommendations were sent to the Committee for Medicinal Products for Human Use (CHMP), which has adopted the Agency's final opinion.

A legally binding decision has been adopted by the European Commission and is applicable in all EU Member States.

In Malta

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 being suspended in the EU. The suspension will follow an agreed timetable.
- Two intravenous linear agents – gadoxetic acid and gadobenic acid – will 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 – will 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 will be updated accordingly.
- Healthcare professionals in Malta were sent a letter with information about EMA's review of gadolinium contrast agents. Archived DHPC letters are available online at http://www.medicinesauthority.gov.mt/dhpc

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.

For more information on EMA's review of Gadolinium contrast agents please refer to the EMA website

Reporting Adverse Drug Reactions

Healthcare professionals and patients are encouraged to maintain vigilance on Gadolinium contrast agents. Suspected Adverse Drug Reactions (side effects) may be reported using the Medicines Authority Form (available from: **http://www.medicinesauthority.gov.mt/adrportal**) and sent by mail to Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000 or email to **postlicensing.medicinesauthority@gov.mt** or to the marketing authorisation holder or their local representatives.

Post-Licensing Directorate
Medicines Authority

Healthcare professionals and patients are encouraged to regularly check the Medicines Authority website for product safety updates as these are issued on an ongoing basis.

Feedback Form

The Medicines Authority thanks you for the time taken to read this safety circular. The dissemination of safety circulars is an important process whereby Regulatory Authorities can communicate important issues with respect to the safety of medicines, in order to protect and enhance public health

The Medicines Authority kindly invites your anonymous feedback about the regulatory action being communicated. This may be returned by folding this formt (address side up), stapling the ends and then posting (no stamp required)

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