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Direct Healthcare Professional Communication

Gadolinium contrast agents: updated recommendations following review of gadolinium retention in brain and other tissues

Dear Healthcare Professional,

In agreement with the European Medicines Agency and the Malta Medicines Authority, Bayer PLC and GE Healthcare AS would like to inform you of the following:

Summary

- A review by the European Medicines Agency (EMA) has confirmed that small amounts of gadolinium are retained in brain tissue after use of gadolinium contrast agents.
- More gadolinium retention in the brain has been observed with linear gadolinium agents than with macrocyclic agents.
- To date, there is no evidence that gadolinium retention in the brain from any agent has caused harm to patients.
- **As the long-term risks of gadolinium retention in brain tissue are unknown, EMA recommended that intravenous linear agents be suspended in the EU, with the exception of gadoxetic acid and gadobenic acid, which will remain available for liver scans only.**
- **The linear agent gadopentetic acid will continue to be available solely for intra-articular use.**
- **Intravenous and intra-articular macrocyclic agents 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.

Overview of recommendations for gadolinium contrast agents authorised in the EU		
Product	**Type (formulation)**	**Authorisation status***
Artirem/Dotarem/Dotarem Arthro (*gadoteric acid*)	macrocyclic (intra-articular)	maintained
Dotarem (*gadoteric acid*)†	macrocyclic (i.v.)	maintained
Gadovist (*gadobutrol*)	macrocyclic (i.v.)	maintained
Magnevist (*gadopentetic acid*)	linear (intra-articular)	maintained
Magnevist (*gadopentetic acid*)‡	linear (i.v.)	suspended
Multihance (*gadobenic acid*)	linear (i.v.)	restricted to liver scans
Omniscan (*gadodiamide*)	linear (i.v.)	suspended
Optimark (*gadoversetamide*)	linear (i.v.)	suspended
Primovist (*gadoxetic acid*)	linear (i.v.)	maintained§
Prohance (*gadoteridol*)	macrocyclic (i.v.)	maintained

* Prescribing information has been updated for products whose authorisations are maintained.
† Plus respective generic products (Cyclolux, Dotagita, Dotagraf, Dotamulti, Dotaspin, DotaVision, Gadoteerzuur Guerbet Gadotersäure Sanochemia).
‡ Plus respective generic products (Gadocon, Gadolan, Gadopent, Gadopentat, Gadopur, Gadothek, Magnegita, Magnetolux, Magnevision, Magnograf, MR-Lux).
§ Gadoxetic acid is only authorised for liver scans.

Background on the safety concern

A comprehensive review by the European Medicines Agency (EMA) found convincing evidence of gadolinium retention in the brain following use of intravenous gadolinium contrast agents for magnetic resonance (MR) scans. The retention has been confirmed by studies measuring gadolinium concentrations with mass spectrometry and by increases in signal intensity in brain tissue seen in MR scans.

More gadolinium retention in the brain has been observed with linear gadolinium agents than with macrocyclic agents.

No evidence of harm to patients has been observed and no adverse neurological effects, such as cognitive or movement disorders, have been attributed to any gadolinium agent. However, the long-term risks of retained gadolinium in the brain are unknown and long-term safety data are limited.

Taking into account all available data, including data from gadolinium retention in other tissues, and views of expert groups, EMA has issued recommendations to prevent any risks that could potentially be associated with gadolinium in the brain.

The marketing authorisations of the intravenous linear agents gadodiamide and gadoversetamide and the intravenous formulation of gadopentetic acid are therefore being suspended.

EMA considered that the benefit-risk balance for the two intravenous linear agents, gadoxetic acid and gadobenic acid, is favourable only for use in liver scans. Both agents are taken up by the liver and can be used for imaging poorly vascularised liver lesions, especially in delayed phase imaging, where macrocyclic agents are not adequate. The marketing authorisation of gadoxetic acid for liver scans is therefore being maintained, while the authorisation for gadobenic acid is being restricted to liver scans.

The intra-articular formulation of gadopentetic acid is being maintained because the dose of gadolinium used for joint injections is low and patients are not likely to need repeated injections.

All macrocyclic agents reviewed – gadobutrol, gadoteric acid and gadoteridol – will remain authorised for their current indications.

As all gadolinium contrast agents may cause gadolinium retention, healthcare professionals are advised to use gadolinium contrast agents only when essential diagnostic information cannot be obtained with unenhanced scans and they should use the lowest doses that provide sufficient enhancement for diagnosis. The product information for gadolinium contrast agents has been updated accordingly.

Call for reporting

Healthcare professionals are reminded to continue to report suspected adverse reactions associated with gadolinium contrast agents in accordance with the national spontaneous reporting system. Any suspected adverse reactions and medication errors can be reported via the national Adverse Drug Reactions (ADRs) reporting system. Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to Medicines Authority Post-licensing, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000, Malta or sent by email to postlicensing.medicinesauthority@gov.mt

Companies contact points

If you have further questions or require additional information please contact:

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Yours faithfully,

Post-Licensing Directorate
Medicines Authority

Disclaimer

This Direct Healthcare Professional Communication has been submitted to you on behalf of Bayer PLC and GE Healthcare AS together with their local representatives.