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Conclusion of European Review of Gadolinium Contrast Agents – Publication of European Commission Decision

The European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) review of the risk of gadolinium deposition in brain tissue following the use of Gadolinium Contrast Agents (GdCAs) in patients undergoing magnetic resonance imaging (MRI) scans has concluded with the publication by the European Commission of a legally binding decision.

The recommendations are as follows:

- The review confirmed that small amounts of gadolinium are retained in brain tissue after use of GdCAs.
- 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 GdCAs 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.

As this relates to marketing authorisations, the following applies:

- The benefit-risk balance of four linear GdCA medicinal products containing **intravenous gadobenic acid** (Multihance) (in all indications other than liver imaging), **gadodiamide** (Omniscan), **gadopentetic acid** (IV presentation) (Magnevist), and **gadoversetamide** (Optimark) is no longer favourable and the marketing authorisations for these products should be **suspended**.
- The benefit-risk balance of linear GdCA medicinal products containing **intravenous gadobenic acid** (Multihance) or **intravenous gadoxetic acid** (Primovist) in the indication of **liver imaging**, and **intra-articular gadopentetic acid** (Magnevist) is **favourable** subject to agreed changes in the product information.
- The benefit-risk balance for all macrocyclic GdCAs on the EU market (**gadoteridol** (Prohance), **gadobutrol** (Gadovist) and **gadoteric acid** (Dotarem)) remains **favourable** for all current indications subject to agreed changes to the product information.

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The review found convincing evidence of accumulation of gadolinium in the brain from both non-clinical and clinical studies with consistent results indicating that linear GdCAs may accumulate in brain tissue and lead to areas of increased signal intensity on MRI scans which may persist for many months following administration. Although no symptoms or disease linked to gadolinium deposition in the brain has been reported, data available on the long term effects in the brain are limited.

The benefit-risk of gadoxetic acid (Primovist) and gadobenic acid (Multihance), a linear GdCA used for the detection of focal liver lesions, remains favourable as it is considered to meet an important diagnostic need in patients with few alternatives and is used in lower dose than other linear GdCAs.

The benefit-risk of **intra-articular** use of gadopentetic acid (Magnevist) remains favourable.

The product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) for the linear GdCAs that will remain on the EU market and that of macrocyclic GdCAs will be updated to guide risk minimisation, namely that they should be used at the lowest dose that enhances images sufficiently to make a diagnoses and only if unenhanced scans are not suitable. A Direct Healthcare Professional Communication has been circulated by the Marketing Authorisation Holders (following approval by the HPRA) to relevant healthcare professionals.

Key Message

A review by the European Medicines Agency (EMA) has confirmed that small amounts of gadolinium are retained in brain tissue after use of GdCAs.

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 GdCAs 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.

All suspected adverse reactions associated with GdCAs should be reported to the HPRA via the various reporting methods available (www.hpra.ie).

Further information is available from www.hpra.ie and www.ema.europa.eu

Correspondence/Comments should be sent to the Pharmacovigilance Section, Health Products Regulatory Authority, contact details below.

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