Dear Healthcare Professionals,

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

Your attention is drawn to the announcement that European Medicines Agency (EMA) has concluded its review of gadolinium contrast agents, confirming recommendations to restrict the use of some linear gadolinium agents used in MRI body scans and suspend the authorizations of others. The recommendations follow a review which 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 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 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.

**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 authorizations 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.
- 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 vascularized hepatic lesions, especially in delayed phase imaging, that cannot be adequately studied with other agents.

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• 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 the EU will also be sent a letter with information about EMA’s review of gadolinium contrast agents.

Please refer to the following website in EMA for details:

In Hong Kong, there are 8 registered pharmaceutical products which are gadolinium contrast agents, and are prescription only medicines, including Magnevist Inj (HK-32608) containing meglumine gadopentetate, Omniscan Inj 0.5mmol/ml (HK-43493) containing gadodiamide, Gadovist Inj 1mmol/ml (HK-51750) and Gadovist Inj 1mmol/ml (Prefilled Syringe) (HK-57330) containing gadobutrol, Primovist Prefilled Syringe Inj 0.25mmol/ml (HK-54116) containing sodium gadoxetate, Dotarem Inj 377mg/ml (Vial) (HK-41578) and Dotarem Prefilled Syringes 377mg/ml (HK-41579) containing meglumine gadoterate, and MultiHance Inj 334mg (HK-57789) containing gadobenic acid (as meglumine gadobenate).

Related news was previously issued by various overseas drug regulatory authorities, and was posted on the Drug Office website since 28 July 2015, with the latest update posted on 8 July 2017. So far, the Department of Health (DH) has received 7 cases of adverse drug reaction (ADR) in connection with gadolinium contrast agents: 2 cases on Omniscan, 3 cases on Dotarem, and 2 cases on Gadovist, but all these ADR cases were not related to gadolinium deposition in brain tissues. In light of the above EMA’s announcement, the DH has contacted the certificate holders of the products containing ingredients recommended by the EMA for suspension or restriction on its use for any action deemed appropriate and the responses are pending. The matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board. Healthcare professionals are advised to balance the risk of possible adverse effects against the benefit of treatment.

Please report any adverse events caused by drugs to the Pharmacovigilance Unit of the DH (tel. no.: 2319 2920, fax: 2319 6319 or email: adr@dh.gov.hk). For details, please refer to the website at Drug Office under "ADR Reporting": http://www.drugoffice.gov.hk/adr.html. You may wish to visit the Drug Office's website for subscription and browsing of "Drug News" which is a monthly digest of drug safety news and information issued by Drug Office.

Yours faithfully,

(Joseph LEE)
for Assistant Director (Drug)

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