DRUG SAFETY INFORMATION No.63

5 March 2018

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Dear Healthcare Professional

RISK OF GADOLINIUM BRAIN DEPOSITS ASSOCIATED WITH USE OF GADOLINIUM-BASED CONTRAST AGENTS

The Health Sciences Authority (HSA), in consultation with its Product Vigilance Advisory Committee (PVAC), would like to update healthcare professionals on the outcome of its review regarding the potential risk of gadolinium deposition in the brain following repeated use of gadolinium-based contrast agents (GBCA). There has been increasing scientific evidence of gadolinium deposition in the brain following the use of GBCAs (particularly the linear agents) during magnetic resonance imaging (MRI) scans. HSA's review concluded that while there is currently no definite evidence of clinical harm of gadolinium brain deposition following GBCA administration, healthcare professionals are advised to use the lowest effective dose of GBCA whenever possible and repeated doses of GBCAs should only be administered after careful benefit-risk assessment.

Background

2 GBCAs are used to enhance the quality of magnetic resonance (MR) images to improve the diagnostic accuracy of the MRI. GBCAs may be categorised according to their chemical structures, namely linear or macrocyclic. Scientific evidence suggests that compared to the macrocyclic agents, the linear agents are more susceptible to the dissociation of the chelate and the subsequent deposition of the free gadolinium in the brain.[1-4]

3 There are six GBCAs registered in Singapore (see **Annex 1)**. All of the GBCAs are indicated for the enhancement of MRI scans of several anatomical structures (e.g. cranial and spinal regions and liver) via intravenous (IV) administration, except for Primovist (gadoxetate disodium), which is approved only for liver MRI scans.

4 Initial brain imaging studies have reported hyperintensities in brain MRI scans of patients who have received multiple GBCAs administrations, leading to the hypothesis that gadolinium is deposited in the brain after repeated GBCA use.[5] This hypothesis was confirmed by post-mortem studies documenting the presence of gadolinium in the harvested brain tissues of deceased individuals who had been exposed to repeated GBCAs during their lifetime.[6-7] In addition, the evidence for gadolinium deposition has been found to be much stronger with the less stable linear GBCAs as compared with the macrocyclic agents, suggesting that the propensity of a GBCA to cause brain deposition could be related to the chemical structure and stability of the GBCA chelate.[2-4] Based on the current available scientific evidence, the presence of gadolinium brain deposits has not been shown to result in clinical adverse effects and the long-term effects are still being studied.

International Regulatory Actions

5 International regulatory health authorities namely, the European Medicines Agency (EMA), United States Food and Drug Administration (US FDA), Health Canada, Australia Therapeutic Goods Administration (TGA) and New Zealand Medsafe have conducted safety reviews on the potential risk of gadolinium brain deposition following administration of GBCAs. While all the reviews of these agencies concluded that there is no clinical harm that can be directly attributed to gadolinium brain deposition, EMA recommended the suspension of the marketing authorisations of three IV linear GBCAs (gadopentetic acid, gadodiamide and gadoversetamide) while restricting the use of the IV formulation of the linear agent

gadobenic acid to liver scans only, as a precautionary measure. No additional restrictions were instituted for macrocyclic GBCAs but EMA advises that they should be used at the lowest doses that enhance images sufficiently and only when unenhanced body scans are not suitable.[8] The other agencies did not suspend the use of linear GBCAs but strengthened the package inserts (PIs) of the approved GBCAs (both linear and macrocyclic) in their jurisdictions to include information on this potential risk.[9-12]

HSA's Benefit-risk Assessment and Advisory

6 HSA's assessment took into consideration findings from the scientific literature, information provided by the drug companies, local usage of GBCAs, expert opinions of the local radiologists and regulatory actions taken by the international regulatory health authorities. A review conducted by the College of Radiologists Singapore had concluded that there is no definitive evidence of Parkinson's disease or other neurological diseases linked to GBCAs. It also stated that GBCAs have a long history of use with clear benefits to patients without major long-term side effects.[13]

7 HSA has assessed that linear GBCAs still have a place in local clinical practice, particularly in specialised MRIs such as liver and cardiac imaging. Scientific evidence has shown that gadolinium accumulates in brain tissues following multiple GBCA administrations, with a tendency towards higher gadolinium deposition with the linear agents as compared with macrocyclic agents. However, no adverse clinical consequences have been identified and the long term clinical significance of gadolinium deposition is presently unknown. To-date, HSA has not received any reports of adverse events arising from the accumulation of gadolinium in brain tissues. While the benefit-risk of linear GBCAs remains favourable, HSA would like to advise healthcare professionals, in particular radiologists of the following, as a precautionary measure:

- Consider the retention characteristics of each GBCA when choosing GBCAs for patients
- Use the lowest effective dose of GBCA whenever possible and repeated doses of GBCAs should only be administered after careful benefit-risk assessment
- Closely monitor patients who have been administered GBCAs and to report any serious adverse events suspected to be associated with GBCA use

8 HSA will be working with the companies to strengthen the local PIs of GBCAs to warn of the potential risk of gadolinium brain deposits. HSA will continue to closely monitor the international and local developments of this issue and update healthcare professionals of any new significant findings.

9 Healthcare professionals are encouraged to report any suspected serious adverse events related to use of GBCAs to the Vigilance and Compliance Branch at Tel: 6866 1111, Fax: 6478 9069, or report online at http://www.hsa.gov.sg/ae_online. Should you have further queries regarding this matter, please contact Ms Leng Xue Zhen at Tel: 6866 3550 or email: leng_xue_zhen@hsa.gov.sg.

Thank you.

Yours faithfully

MS JALENE POH
DIRECTOR
VIGILANCE AND COMPLIANCE BRANCH
HEALTH PRODUCTS REGULATION GROUP
HEALTH SCIENCES AUTHORITY

cc Director of Medical Services, Ministry of Health
Chief Executive Officer, Health Sciences Authority

Annex 1

Table 1. Registered GBCAs in Singapore

Brand Name	Active Ingredient	Company	Type
Dotarem	Gadoteric acid	Kenda	Macrocyclic
Gadovist	Gadobutrol	Bayer	Macrocyclic
Primovist	Gadoxetate disodium	Bayer	Linear
Multihance	Gadobenate dimeglumine	LF Asia	Linear
Magnevist	Gadopentetate dimeglumine	Bayer	Linear
Omniscan	Gadodiamide	GE Healthcare	Linear

References

1. *J Magn Reson Imaging. 2017;46:338-53.*
2. *Radiology. 2015;3:803-9.*
3. *Eur Radiol. 2017;27(8):3353-61.*
4. *Radiology. 2015;275(3):783-91.*
5. *Radiology. 2014;270(3):834-41.*
6. *Radiology. 2015;275(3):772-82.*
7. *Radiology. 2015;276(1):228-32.*
8. *http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/gadolinium_contrast_agents_31/Opinion_provided_by_Committee_for_Medicinal_Products_for_Human_Use/WC500231824.pdf*
9. *https://www.fda.gov/Drugs/DrugSafety/ucm589213.htm*
10. *http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2017/61676a-eng.php*
11. *https://www.tga.gov.au/alert/gadolinium-based-contrast-agents-mri-scans*
12. *http://www.medsafe.govt.nz/safety/EWS/2017/GadoliniumContrastAgents.asp*
13. *http://ams.edu.sg/view-pdf.aspx?file=media%5c4087_fi_750.pdf&ofile=Advisory+on+Linear+Gadolinium-Based+Contrast+Agents_FINAL.pdf*

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