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Dear Healthcare Professionals,

Gadolinium-based contrast agents: Assessing the potential risks of congenital anomalies, stillbirth and neonatal death

Your attention is drawn to the Health Canada's announcement that it reviewed the potential risks of congenital anomalies, stillbirth and neonatal death with the use of gadolinium-based contrast agents (GBCAs) during pregnancy. This safety review was initiated following updates made by the United States Food and Drug Administration to the product information for all GBCAs to include the potential risks of stillbirth and neonatal death with the use of these agents during pregnancy.

At the time of the review, the Canadian Product Monographs (CPMs) for GBCAs include warnings to limit the use of these agents during pregnancy unless the potential benefit justifies the potential risk to the fetus, and that the use of a specific type of GBCA may be preferable during pregnancy. The purpose of this review was to assess whether additional warnings or other actions were required in Canada.

GBCAs are classified into 2 types based on their chemical structure: linear agents and macrocyclic agents. In 2019, the majority of GBCAs used in Canada were of the macrocyclic type, which may be preferable in pregnancy. There are currently 8 GBCAs authorized for sale in Canada:

- Linear agents: Magnevist (gadopentetate dimeglumine) and 1 generic drug product, MultiHance (gadobenate dimeglumine), Omniscan (gadodiamide), Primovist (gadoxetate disodium)
- Macrocyclic agents: Dotarem (gadoterate meglumine), Gadovist (gadobutrol), ProHance (gadoteridol)

Health Canada reviewed information from searches of the Canada Vigilance database, the World Health Organization's Adverse Drug Reaction Database, and the published literature. At the time of the review, Health Canada had not received any Canadian or international reports of stillbirth nor neonatal death with the use of GBCAs during pregnancy. Health Canada reviewed 3 international case reports of congenital anomalies with the use of GBCAs from the Canada Vigilance database. There were no

Canadian reports of congenital abnormalities related to GBCA use at the time of the assessment. The review concluded it was unlikely that congenital anomalies were linked to GBCA use during pregnancy for 1 case, while 2 cases did not have enough information in the reports for further review.

Health Canada also looked at additional information from 7 published studies on the use of GBCAs in pregnancy and congenital anomalies, stillbirth and neonatal death. One large Canadian study found a higher risk of stillbirth or neonatal death with the use of GBCAs during pregnancy. However, it was not possible to conclude there was a link between these potential risks and the use of GBCAs during pregnancy due to weaknesses in the study design. The other 6 studies did not support a link between congenital anomalies, stillbirth, or neonatal death and the use of GBCAs in pregnancy. These studies also had weaknesses in their design.

Health Canada's review of the available information found no link between the use of GBCAs during pregnancy and the risk of congenital anomalies. However, at this time, there is not enough information to rule out a link between the use of GBCAs during pregnancy and the risk of stillbirth and neonatal death. As a precaution, given the potential for serious harm to fetuses and infants, Health Canada will work with the manufacturers of these products to include the potential risks of stillbirth and neonatal death in the CPMs for all GBCAs.

Please refer to the following website in Health Canada for details:
https://hpr-rps.hres.ca/reg-content/summary-safety-review-detail.php?lang=en&linkID=SSR00273

In Hong Kong, there are 10 registered pharmaceutical products which are gadolinium-based contrast agents (GBCAs), namely Dotarem Inj 377mg/ml (Vial) (HK-41578), Dotarem Prefilled Syringes 377mg/ml (HK-41579), Dotagraf Solution For Injection 22.62g/60ml (HK-66545), Dotagraf Solution For Injection 3.77g/10ml (HK-66546) and Dotagraf Solution For Injection 7.54g/20ml (HK-66547) containing meglumine gadoterate, 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 Pre-filled Syringe Inj 0.25mmol/ml (HK-54116) containing sodium gadoxetate, MultiHance Inj 334mg (HK-57789) containing gadobenic acid (as meglumine gadobenate). All products are prescription-only medicines.

So far, the Department of Health (DH) has received adverse drug reaction related to Dotarem (3 cases), Omniscan (2 cases), Gadovist (3 cases) and Primovist (one case), but these cases are not related to congenital anomalies, stillbirth or neonatal death.

In light of the above Health Canada's announcement, 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 Adverse Drug Reaction 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,

(Ling PANG)
for Assistant Director (Drug)