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DEPARTMENT OF HEALTH
DRUG OFFICE
DRUG INFORMATION AND PHARMACOVIGILANCE DIVISION
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(來函請敍明此檔案號碼) DH DO DIMC/7-30/1
(IN REPLY PLEASE QUOTE THIS FILE REF.)

20 Jul 2022

Dear Healthcare Professionals,

Cholinesterase inhibitors (donepezil-, rivastigmine- and galantamine-containing products): Assessing the potential risk of QT interval prolongation and torsade de pointes

Your attention is drawn to the Health Canada's announcement that it reviewed the risk of QT interval prolongation and torsade de pointes with the use of cholinesterase inhibitors. This safety review was initiated when Health Canada learned that the European Medicines Agency had updated the product safety information related to this risk for 2 cholinesterase inhibitors (donepezil and galantamine).

At the time of review, the Canadian product monograph (CPM) for cholinesterase inhibitors included differing information about QT interval prolongation and/or torsade de pointes. The purpose of this review was to assess whether additional warnings or other actions for QT interval prolongation and torsade de pointes were required in Canada.

Health Canada reviewed the available information from searches of the Canada Vigilance database, international databases and published literature. Health Canada reviewed 53 case reports (1 Canadian, 52 international) of QT interval prolongation and torsade de pointes in patients taking cholinesterase inhibitors. Of the 53 reports, 35 were for donepezil, 10 (1 Canadian) for galantamine, and 8 for rivastigmine. For donepezil, 2 cases were found to be probably linked, 30 cases were possibly linked, 2 cases were unlikely to be linked and 1 case could not be assessed. Four deaths were reported (2 of which were determined to have a possible link and 2 unlikely to be linked). For galantamine, 3 cases were found to be probably linked, 5 cases were possibly linked, 1 case was unlikely to be linked and 1 case (Canadian) could not be assessed. One death was reported and was unlikely to be linked. For rivastigmine, 7 cases were found to be possibly linked and 1 case was unlikely to be linked. Health Canada also reviewed 20 articles published in the scientific literature. There was limited evidence to support a link between the use of cholinesterase inhibitors and the risk of QT interval prolongation and torsade de pointes in these articles.

Health Canada's review supported a link between the use of all 3 cholinesterase inhibitors and the

risk of QT interval prolongation and torsade de pointes, and determined that product information updates were warranted. Health Canada will work with the manufacturers of all cholinesterase inhibitors to strengthen the information in the CPMs about the risk of QT interval prolongation and torsade de pointes. This update will also advise that the risk is increased in patients with a history of certain heart conditions; a history or family history of QT interval prolongation; low levels of certain electrolytes, such as magnesium, potassium or calcium in the blood; or taking certain medications that can affect heart rhythm at the same time as the cholinesterase inhibitors.

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=SSR00285

In Hong Kong, there are registered pharmaceutical products containing donepezil (35 products), rivastigmine (30 products) and galantamine (10 products). All products are prescription-only medicines. So far, the Department of Health (DH) has not received any case of adverse drug reaction related to donepezil. The DH has received adverse drug reaction related to rivastigmine (one case) and galantamine (one case), but these cases were not related to QT interval prolongation and torsade de pointes. News related to cardiac conduction disorders (including QT interval prolongation and torsade de pointes) associated with the use of donepezil was previously issued by Australia Therapeutic Goods Administration, and was posted on the Drug Office website on 1 Mar 2022. Letters to inform local healthcare professionals were issued by the DH on the same day. In light of the above Health Canada's announcement, the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Please note that this letter serves as a means for the DH to communicate important new safety information about registered pharmaceutical products with healthcare professionals in Hong Kong and is not intended to serve as guidelines or to replace professional clinical judgement. 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,

(Terence MAN)
for Assistant Director (Drug)