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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.)

DEPARTMENT OF HEALTH
DRUG OFFICE
DRUG INFORMATION AND
PHARMACOVIGILANCE DIVISION
Suites 2002-05, 20/F, AIA Kowloon Tower,
Landmark East, 100 How Ming Street,
Kwun Tong, Kowloon, Hong Kong

18 Jan 2023

Dear Healthcare Professionals,

Third generation aromatase inhibitors (anastrozole, exemestane, letrozole): Assessing the potential risk of tendon disorders

Your attention is drawn to the Health Canada's announcement that it reviewed the evidence for the risks of tendonitis, tenosynovitis, and tendon rupture related to the use of third generation aromatase inhibitors to determine whether regulatory actions would be required in Canada. The safety review was triggered by a labelling update for letrozole, to include the risks of tendonitis and tendon rupture, in Europe. While the European Medicines Agency's safety assessment was limited to letrozole, it did not rule out the possibility that the risk of tendon disorders may be associated with all third generation aromatase inhibitors. At the time of the review, the Canadian product monographs (CPMs) for third generation aromatase inhibitors included information on the risk of tenosynovitis of the hands.

A tendon is a rope-like fibrous tissue that attaches muscle to bone. A thin fibrous sheath surrounds the tendon. Disorders of the tendon include tendon inflammation (tendonitis), tendon tears (tendon rupture) and inflammation of the tendon sheath (tenosynovitis). Tendon disorders can cause serious physical limitations and, in some cases, require surgery.

Health Canada reviewed information from published and unpublished population-based studies and case reports of individual patients. Information was obtained from searches of international databases of published literature, drug manufacturers, as well as searches of the Canada Vigilance database. Health Canada reviewed 5 randomized controlled trials (RCTs) that included a total of 28,873 patients. Reported events of tendonitis and tenosynovitis, which were uncommon in occurrence (less than 1%), were found to be likely linked to the use of third generation aromatase inhibitors. A link with tendon rupture, which was rare in occurrence (less than 0.1%), could not be ruled out. Health Canada also reviewed 25 case reports (2 Canadian and 23 international) of tendon rupture (10 cases) and tendonitis (15 cases). Health Canada did not review case reports of tenosynovitis as there was insufficient information in these reports to separate tenosynovitis from other labelled adverse events involving the muscles and bones. Of the 10

reported cases of tendon rupture, 4 involved the use of anastrozole, 4 letrozole and 2 exemestane (1 Canadian). Of the 15 reported cases of tendonitis, 7 involved the use of anastrozole (1 Canadian), 4 involved letrozole and 4 exemestane. Across the assessed cases, tendonitis and tendon rupture affected both upper and lower limbs. These 25 case reports included other medications and/or conditions that could have contributed to the reported adverse events. From these case reports, a link between the risk of tendon rupture and tendonitis with the use of a third generation aromatase inhibitor could not be ruled out.

Health Canada's review of the available RCTs and case reports concluded that there is likely a link between the use of third generation aromatase inhibitors and the risks of tendonitis and tenosynovitis, which were uncommon in occurrence. A link with tendon rupture, which was rare in occurrence, could not be ruled out. Health Canada is working with the manufacturers of third generation aromatase inhibitors to update the CPMs to include these risks.

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=SSR00289

In Hong Kong, there are registered pharmaceutical products containing anastrozole (16 products), exemestane (7 products) and letrozole (14 products). All products are prescription-only medicines. So far, the Department of Health (DH) has received adverse drug reaction related to anastrozole (one case), exemestane (7 cases) and letrozole (40 cases), but these cases were not related to tendon disorders. 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)