衞生署藥物辦公室
藥物註冊及進出口管制部
香港九龍南昌街 382 號公共衞生檢測中心二樓
2319 8458
電話號碼 Tel. No.:
查詢處 Enquiries (852) 2319 8456
傳真號碼 Faxline No. (852) 2803 4962

DEPARTMENT OF HEALTH
DRUG OFFICE
DRUG REGISTRATION AND IMPORT/EXPORT CONTROL DIVISION
3/F., Public Health Laboratory Centre,
382 Nam Cheong Street, Kowloon, Hong Kong

BY FAX

本署檔號 OUR REF.: DH DO PRIE/7-30/15

15 December 2015

(來函請註明此檔案號碼)
(IN REPLY PLEASE QUOTE THIS FILE REF.)

Dr. Donald LI
President
Hong Kong Academy of Medicine
(Fax Number: 2505 5577)

Dear Dr. LI,

Antiretroviral medicines: updated advice on body-fat changes and lactic acidosis

Your attention is drawn to the Medicines and Healthcare products Regulatory Agency's (MHRA) announcement regarding updated advice on fat redistribution and lactic acidosis associated with antiretrovirals for HIV treatment.

In the UK, warnings regarding lipodystrophy and lactic acidosis were introduced in product information for antiretrovirals for HIV treatment in the early 2000s in line with clinical findings. Class warnings for lactic acidosis applied only to nucleoside and nucleotide analogue medicines, whereas lipodystrophy warnings applied to all antiretroviral agents.

An EU-wide review therefore looked at the appropriateness and applicability of the warnings to these products. The review of the risk of lipodystrophy included lipoatrophy, lipoaccumulation, and changes in weight and metabolism.

Lipoatrophy was previously considered to be associated with nucleoside reverse transcriptase inhibitors (NRTIs). The review noted that lipoatrophy was associated with reduced mitochondria levels in fat cells, and related only to substances with a high risk of mitochondrial toxicity—ie, zidovudine, stavudine, and possibly didanosine. However, lipoatrophy was not seen in regimens with other NRTI products: instead, treatment was associated with fat gain from improved HIV infection control.

As for lipoaccumulation, there was no clear evidence that disproportional body-fat redistribution was related to antiretroviral treatment.

As for blood-lipid levels (changes in weight and metabolism), warnings of increased levels of blood lipids were previously included in the product information for protease inhibitors and for nucleoside and nucleotide analogues. Protease inhibitors were also thought to be associated with a risk of hyperglycaemia. Effects on blood lipids and glucose may occur with any HIV medicine.

Consistent with current HIV treatment guidelines, product information will be amended to advise that weight gain and metabolic changes (such as lipid and glucose increases) may occur during treatment with any HIV medicine. However, these changes are partly linked to underlying disease control and lifestyle in addition to antiretroviral treatment. Warnings for lipoatrophy and lipoaccumulation will be retained only for zidovudine, stavudine, and didanosine.

As for lactic acidosis, warnings about the risk of lactic acidosis were previously applicable only to nucleoside and nucleotide analogues. The review looked at evidence from observational studies published case reports, and data from licence holders of antiretroviral medicines. The risk of lactic acidosis was considered to differ across the class, being most strongly associated with zidovudine, stavudine, and didanosine.

Therefore, in line with current evidence, warnings about lactic acidosis will be removed for nucleoside and nucleotide analogues, with the exception of products that contain zidovudine, stavudine, or didanosine. For combination medicines, any warnings still relevant to any of the active substances will remain in the medicine's product information.

Advice for healthcare professionals is as follows:

- Product information for antiretrovirals will be updated in the UK to reflect current knowledge about lipodystrophy (including lipoatrophy) and lactic acidosis, so that patients and healthcare professionals can decide on treatment based on the most up-to-date advice.
- There are no new risks or safety concerns associated with antiretrovirals. Patients can be reassured that previous information about the risk of lipodystrophy and lactic acidosis for several medicines is no longer considered relevant.

Please refer to the MHRA's website for details:

https://www.gov.uk/drug-safety-update/antiretroviral-medicines-updated-advice-on-body-fat-changes-and-lactic-acidosis#blood-lipid-levels-changes-in-weight-and-metabolism

In Hong Kong, there are 15 registered pharmaceutical products containing zidovudine, 6 products containing stavudine, and 2 products containing didanosine. All these products are prescription-only medicines. So far, DH has received two adverse drug reaction cases related to stavudine, but they were not related to lipodystrophy and/or lactic acidosis. DH will continue to remain vigilant on the safety of antiretroviral medicines. 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 sincerely,

(Grant NG)
for Assistant Director (Drug)