衞生署藥物辦公室
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DEPARTMENT OF HEALTH
DRUG OFFICE
DRUG REGISTRATION AND IMPORT/EXPORT CONTROL DIVISION
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BY FAX

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

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

Dear Dr. LI,

Direct-acting antivirals for hepatitis C: risk of hepatitis B reactivation

Your attention is drawn to the U.S. Food and Drug Administration's (FDA) announcement regarding the risk of hepatitis B virus (HBV) reactivation in any patient who has a current or previous infection with HBV and is treated with certain direct-acting antiviral (DAA) medicines for hepatitis C virus. In a few cases, HBV reactivation in patients treated with DAA medicines resulted in serious liver problems or death.

As a result, FDA is requiring a Boxed Warning, the most prominent warning, about the risk of HBV reactivation to be added to the drug labels of these DAAs directing healthcare professionals to screen and monitor for HBV in all patients receiving DAA treatment. This warning will also be included in the patient information leaflet or Medication Guides for these medicines.

DAA medicines are used to treat chronic hepatitis C virus (HCV) infection, an infection that can last a lifetime. These medicines reduce the amount of HCV in the body by preventing HCV from multiplying, and in most cases, they cure HCV. Without treatment, HCV can lead to serious liver problems including cirrhosis, liver cancer, and death.

FDA identified 24 cases of HBV reactivation reported to FDA and from the published literature in HCV/HBV co-infected patients treated with DAAs during the 31 months from November 22, 2013 to July 18, 2016. This number includes only cases submitted to FDA, so there are likely additional cases about which FDA is unaware. Of the cases reported, two patients died and one required a liver transplant. HBV reactivation was not reported as an adverse event in the clinical trials submitted for the DAA approvals because patients with HBV co-infection were excluded from the trials. The trials excluded these patients in order to specifically evaluate the safety of DAAs, including their effects on the liver, in patients infected with only HCV and without the presence of another virus which affects the liver.

It is currently unknown why the reactivation occurs. FDA advised healthcare professionals to:

- Screen all patients for evidence of current or prior HBV infection before initiating treatment with DAAs by measuring HBsAg and anti-HBc. In patients with serologic evidence of HBV infection, measure baseline HBV DNA prior to DAA treatment.
- Monitor patients who show evidence of current or prior HBV infection for clinical and laboratory signs (i.e., HBsAg, HBV DNA, serum aminotransferase levels, bilirubin) of hepatitis flare or HBV reactivation during DAA treatment and post-treatment follow-up.
- Consult a physician with expertise in managing hepatitis B regarding the monitoring and consideration for HBV antiviral treatment in HCV/HBV co-infected patients.

- Counsel patients to contact a healthcare professional immediately if they develop fatigue, weakness, loss of appetite, nausea and vomiting, yellow eyes or skin, or light-colored stools, as these may be signs of serious liver injury.

Please refer to the FDA's website for details:

http://www.fda.gov/Drugs/DrugSafety/ucm522932.htm

In Hong Kong, there are four registered pharmaceutical products which are DAA medcines, namely Harvoni Tablets [sofosbuvir/ ledipasvir (HK-63886)] and Sovaldi Tablets 400mg [sofosbuvir (HK-63501)] which are registered by Gilead Sciences Hong Kong Limited, Viekira Pak Tablets [ombitasvir/ paritaprevir/ ritonavir/ dasabuvir (HK-63695)] which is registered by Abbvie Limited, and Daklinza Tablets 60mg [daclatasvir (HK-64505)] which is registered by Bristol-Myers Squibb Pharma (HK) Ltd. All these products are prescription only medicines. There is no registered pharmaceutical product containing simeprevir, velpatasvir, elbasvir or grazoprevir.

Related news on review to assess the extent of HBV reactivation and risk of liver cancer in patients treating with DAA was issued by the EMA, and was posted on the Drug Office website on 21 March and 18 April 2016. The letter to healthcare professionals to draw their attention on the EMA review was issued on 18 April 2016. So far, the Department of Health (DH) has not received any adverse drug reaction report of HBV reactivation in connection with any DAA medicines. In view of the addition of Boxed Warning by FDA, the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board (the Committee). DH will remain vigilant on the conclusion of the EMA review and the information will also be forwarded to the Committee for consideration. 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,

(Joseph LEE)
for Assistant Director (Drug)