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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

16 August 2017

Dear Healthcare Professionals,

Ibrutinib (Imbruvica▼): reports of ventricular tachyarrhythmia; risk of hepatitis B reactivation and of opportunistic infections

Your attention is drawn to the United Kingdom Medicines and Healthcare products Regulatory Agency's (MHRA) announcement that a routine European review examined the safety profile of ibrutinib. Data from randomised controlled trials and the scientific literature were assessed. Worldwide spontaneous suspected adverse drug reaction (ADR) reports were also reviewed from a cumulative post-marketing exposure of approximately 38,000 patient-years.

Regarding ventricular tachyarrhythmia, randomised controlled trials reported a slightly increased risk of ventricular tachyarrhythmia with ibrutinib. In a 2017 study of case reports of relevant events from post-marketing sources and clinical trial data, the authors identified 11 cases of ventricular tachycardia/ventricular fibrillation and 6 cases of sudden cardiac death in patients exposed to ibrutinib. In 12 of these 17 cases, the events occurred without any evidence of prior cardiac history. The review also identified 2 spontaneous ADRs of ventricular tachyarrhythmia in which the role of ibrutinib could not be excluded. The product information of ibrutinib is being updated to include ventricular tachyarrhythmia as a common adverse reaction (thought to occur in fewer than 10 in 100 patients taking ibrutinib post-marketing).

Regarding hepatitis B virus reactivation, data were not available from clinical trials since all patients had been pre-screened for hepatitis B status and those who tested positive were excluded from studies. The review identified 8 cases of hepatitis B reactivation in which the role of ibrutinib was considered probable or possible. The product information of ibrutinib is being updated to include hepatitis B virus reactivation as an uncommon adverse reaction.

Regarding opportunistic infections, infections are a frequent co-morbidity in patients with the haematological malignancies in which ibrutinib is indicated. The review identified 157 cases of aspergillosis among patients exposed to ibrutinib in post-marketing settings, 43 of which were fatal. The review also identified 44 cases of Pneumocystis Jirovecii pneumonia (PJP), none of which were fatal. In clinical trials, ibrutinib did not appear to raise the risk of aspergillosis or PJP compared with comparator treatments. The product information for ibrutinib already lists opportunistic infections as very common adverse reactions (thought to affect more than 10 in 100 patients taking the drug post-marketing).

Healthcare professionals are advised:

- cases of ventricular tachyarrhythmia have been reported;
- temporarily discontinue ibrutinib in patients who develop symptoms suggestive of ventricular arrhythmia, including palpitations, chest pain, dyspnoea, dizziness, or fainting, and assess benefit-risk before restarting therapy;
- be aware of the risk of hepatitis B virus reactivation and establish hepatitis B virus status before initiating therapy;
- for patients with positive hepatitis B serology, consultation with a liver disease expert is recommended before the start of treatment; monitor and manage patients according to local medical standards of care to minimise the risk of hepatitis B virus reactivation; and
- consider prophylaxis according to standard of care for patients who are at an increased risk of opportunistic infections.

Please refer to the following website in MHRA for details:

<https://www.gov.uk/drug-safety-update/ibrutinib-imbruvica-reports-of-ventricular-tachyarrhythmia-risk-of-hepatitis-b-reactivation-and-of-opportunistic-infections>

In Hong Kong, there is one pharmaceutical product containing ibrutinib, namely Imbruvica Capsules 140mg (HK-64088) which is registered by Johnson & Johnson (Hong Kong) Ltd, and is a prescription-only medicine. So far, the Department of Health (DH) has received 7 cases of adverse drug reaction related to ibrutinib, but these cases were not related to ventricular tachyarrhythmia, hepatitis B reactivation or opportunistic infections. 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 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 faithfully,



(Joseph LEE)

for Assistant Director (Drug)