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

31 October 2022

Dear Healthcare Professionals,

EMA recommends measures to minimize risk of serious side effects with Janus kinase inhibitors for chronic inflammatory disorders

Your attention is drawn to the European Medicines Agency's (EMA) announcement that its Pharmacovigilance Risk Assessment Committee (PRAC) has recommended measures to minimise the risk of serious side effects associated with Janus kinase (JAK) inhibitors used to treat several chronic inflammatory disorders. These side effects include cardiovascular conditions, blood clots, cancer and serious infections.

The Committee recommended that these medicines should be used in the following patients only if no suitable treatment alternatives are available: those aged 65 years or above, those at increased risk of major cardiovascular problems (such as heart attack or stroke), those who smoke or have done so for a long time in the past and those at increased risk of cancer.

The Committee also recommended using JAK inhibitors with caution in patients with risk factors for blood clots in the lungs and in deep veins (venous thromboembolism, VTE) other than those listed above. Further, the doses should be reduced in some patient groups who may be at risk of VTE, cancer or major cardiovascular problems.

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The recommendations follow a review of available data, including the final results from a clinical trial1 of the JAK inhibitor Xeljanz (tofacitinib) and preliminary findings from an observational study involving Olumiant (baricitinib), another JAK inhibitor. During the review, the PRAC sought advice from an expert group of rheumatologists, dermatologists, gastroenterologists and patient representatives.

The review confirmed Xeljanz increases the risk of major cardiovascular problems, cancer, VTE, serious infections and death due to any cause when compared with TNF-alpha inhibitors. The PRAC has now concluded that these safety findings apply to all approved uses of JAK inhibitors in chronic inflammatory disorders (rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, axial spondyloarthritis, ulcerative colitis, atopic dermatitis and alopecia areata).

The product information for JAK inhibitors used to treat chronic inflammatory disorders will be updated with the new recommendations and warnings. In addition, the educational material for patients and healthcare professionals will be revised accordingly. Patients who have questions about their treatment or their risk of serious side effects should contact their doctor.

The Janus kinase inhibitors subject to this review are Cibinqo (abrocitinib), Jyseleca (filgotinib), Olumiant (baricitinib), Rinvoq (upadacitinib) and Xeljanz (tofacitinib). These medicines are used to treat several chronic inflammatory disorders (rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, axial spondyloarthritis, ulcerative colitis, atopic dermatitis and alopecia areata). The active substances in these medicines work by blocking the action of enzymes known as Janus kinases. These enzymes play an important role in the process of inflammation that occurs in these disorders. By blocking the enzymes' action, the medicines help reduce the inflammation and other symptoms of these disorders.

Some JAK inhibitors (Jakavi and Inrebic) are used to treat myeloproliferative disorders; the review did not include these medicines. The review also did not cover the use of Olumiant in the short-term treatment of COVID-19, which is under assessment by EMA.

The PRAC recommendations will now be sent to the EMA's Committee for Medicinal Products for Human Use (CHMP) which will issue a final legally binding decision applicable in all European Union Member States.

Please refer to the following website in EMA for details:

https://www.ema.europa.eu/en/news/ema-recommends-measures-minimise-risk-serious-side-effects-janus-kinase-inhibitors-chronic

In Hong Kong, there are 3 registered pharmaceutical products containing tofacitinib, namely Xeljanz Tablets 5mg (HK-63303), Xeljanz XR Extended Release Tablets 11mg (HK-66141) and Xeljanz Tablets 10mg (HK-66833) registered by Pfizer Corporation Hong Kong Limited; 2 products containing baricitinib, namely Olumiant Tablets 2mg (HK-65663) and Olumiant Tablets 4mg (HK-65664) registered by Eli Lilly Asia, Inc.; and 2 products containing upadacitinib, namely Rinvoq Prolonged-Release Tablets 30mg (HK-67512) and Rinvoq Prolonged-Release Tablets 15mg (HK-66872) registered by Abbvie Limited. All products are prescription-only medicines. There is no registered pharmaceutical product containing abrocitinib or filgotinib.

So far, the Department of Health (DH) has received 9 cases of adverse drug reaction related to tofacitinib, of which 2 case were related to cancer, 3 cases were related to deep vein thrombosis, one case was related to pneumonia, one case was related to herpes zoster disseminated, one case was related to cellulitis and one case was related to disseminated tuberculosis. The DH has received 3 cases of adverse drug reaction related to baricitinib, of which one case was related to deep vein thrombosis, one case was related to hypotension and one case was related to pneumocystis jirovecii pneumonia. The DH has received 6 cases of adverse drug reaction related to upadacitinib, of which one case was related to lung inflammation, 4 cases were related to herpes zoster and one case was related to cytomegalovirus colitis.

Related news on the risk of blood clots and death of tofacitinib was previously issued by various overseas drug regulatory authorities, and was posted on the Drug Office website since 26 Feb 2019, with the latest update posted on 17 Sep 2022. Letters to inform local healthcare professionals were issued by the DH on 29 Jul 2019 and 19 Jun 2020. In Dec 2019, the Registration Committee of the Pharmacy and Poisons Board discussed the matter, and decided that the sales pack or package insert of tofacitinib products should include safety information about increased risk of blood clots and death with higher dose (10 mg twice daily).

Related news on the risk of serious heart-related problems and cancer of tofacitinib was previously issued by various overseas drug regulatory authorities, and was posted on the Drug Office website since 5 Feb 2021, with the latest update posted on 17 Sep 2022. Letters to inform local healthcare professionals were issued by the DH on 15 Jun 2021. As previously reported, the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Related news on the risk of blood clots of baricitinib was previously issued by various overseas drug regulatory authorities, and was posted on the Drug Office website since 19 Mar 2020, with the latest update posted on 17 Sep 2022. The current local product inserts already contain safety information on the risk of venous thromboembolism.

In light of the above EMA'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,

pp (Terence MAN)
for Assistant Director (Drug)