Dear Healthcare Professionals,

Nivolumab and pembrolizumab: reports of organ transplant rejection

Your attention is drawn to the UK Medicines and Healthcare products Regulatory Agency’s (MHRA) announcement that there have been reports of rejection of solid organ transplants in patients treated with nivolumab (Opdivo\textsuperscript{T}) or pembrolizumab (Keytruda\textsuperscript{T}). Ipilimumab (Yervoy\textsuperscript{T}) may also interfere with immunosuppressive therapy, increasing the risk of graft rejection.

A European review of worldwide data concluded that nivolumab and pembrolizumab may increase the risk of rejection in organ transplant recipients. The review assessed all cases received up to November 2016 and identified 9 patients who had transplant rejection after receiving nivolumab and pembrolizumab. Of the 5 patients receiving nivolumab, 3 had kidney transplant rejection, 1 had corneal transplant rejection, and 1 had skin graft rejection. Four patients receiving pembrolizumab had kidney transplant rejection; 2 patients were diagnosed after biopsy. In 2 of the 9 reports of rejection, patients started treatment with ipilimumab before receiving nivolumab or pembrolizumab. Ipilimumab is known to increase the risk of graft rejection.

Healthcare professionals are advised:

- rejection of solid organ transplants, including renal and corneal grafts, has been reported in the post-marketing setting in patients treated with programmed death receptor 1 (PD-1) inhibitors
- consider the benefit of treatment with nivolumab or pembrolizumab versus the risk of possible organ transplant rejection for each patient
- some cases of rejection occurred in association with ipilimumab, which carries a warning that it may interfere with immunosuppressive therapy, resulting in an increased risk of graft rejection

Please refer to the following website in MHRA for details: https://www.gov.uk/drug-safety-update/nivolumab-opdivo-pembrolizumab-keytruda-reports-of-organ-transplant-rejection
In Hong Kong, there are 2 pharmaceutical products containing nivolumab, namely Opdivo Concentrate For Solution For Infusion 40mg/4ml (HK-64231) and Opdivo Concentrate For Solution For Infusion 100mg/10ml (HK-64232) which are registered by Bristol-Myers Squibb Pharma (HK) Ltd, 2 products containing pembrolizumab, namely Keytruda Solution For Injection 100mg/4ml (HK-64228) and Keytruda Powder For Injection 50mg (HK-64229) which are registered by Merck Sharp & Dohme (Asia) Ltd, and 2 products containing ipilimumab, namely Yervoy Concentrate For Solution For Infusion 50mg/10ml (HK-63494) and Yervoy Concentrate For Solution For Infusion 200mg/40ml (HK-63495) which are registered by Bristol-Myers Squibb Pharma (HK) Ltd. All of the above products are prescription-only medicines.

So far, the Department of Health (DH) has received 27 cases of adverse drug reaction related to nivolumab, 23 cases related to pembrolizumab and 8 cases related to ipilimumab, but none of them was related to organ transplant rejection. In view of MHRA's reports, the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board and DH will remain vigilant on safety update of the drugs issued by other overseas drug regulatory authorities. 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)