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本署檔號 OUR REF.: DH DO PRIE/7-30/15

(來函請註明此檔案號碼)

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Dear Healthcare Professionals,



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 June 2016

Topical miconazole (including oral gel) and warfarin: reminder of potential for serious interactions

Your attention is drawn to the Medicines and Healthcare products Regulatory Agency's (MHRA) announcement regarding the potential for serious interactions of topical miconazole (including oral gel) with warfarin.

Miconazole (Daktarin, Daktacort) is an antifungal indicated for prevention and treatment of various infections of the mouth, throat, skin, nails, or genitals. It is usually applied topically as a cream, ointment, powder, or oral gel.

Warfarin is an oral anticoagulant that has been widely used since the 1950s for prophylaxis of thromboembolic events. Daily dose depends on individual requirements, and patients receiving long-term therapy require regular coagulation tests.

The potential for drug interactions between miconazole and warfarin is well established. The mechanism is understood to be inhibition by miconazole of one of the main cytochrome P450 isozymes involved in warfarin metabolism (CYP2C9), resulting in reduced warfarin clearance and an enhanced anticoagulant effect.

In the UK, prescribing information for products that contain miconazole warns that because miconazole inhibits CYP2C9, caution should be exercised for patients on oral anticoagulants such as warfarin, and the anticoagulant effect monitored (warfarin dose reduction may be needed).

Up to 13 April 2016, the MHRA has received 146 Yellow Cards that report possible drug interactions between miconazole and warfarin. Most reports (128, 88%) concerned the oral gel form of miconazole. The most frequently reported events were: increased international normalised ratio (INR, 111 reports); contusion (21); haematuria (17); and epistaxis (8). Approximately half of the 146 cases reported an INR increase above 10—ie, the patient was at significantly increased risk of bleeding events (the target INR range for a patient on long-term warfarin therapy is usually between 2 and 3). In 3 cases, a fatal outcome was reported as a result of a haemorrhagic event.

The MHRA is currently reviewing available data for this interaction to determine whether further measures are required to minimise the risks to patients.

Healthcare professionals are reminded that miconazole, including the topical gel formulation, can enhance the anticoagulant effect of warfarin—if miconazole and warfarin are used concurrently, the anticoagulant effect should be carefully monitored and, if necessary, the dose of warfarin reduced. Patients should be advised to tell their doctor or pharmacist if they are receiving warfarin before using products that contain miconazole (including those available without prescription), and to seek medical advice if they notice signs of over-anticoagulation during treatment, such as sudden unexplained bruising, nosebleeds or blood in the urine.

Please refer to the MHRA's website for details:

<https://www.gov.uk/drug-safety-update/topical-miconazole-including-oral-gel-reminder-of-potential-for-serious-interactions-with-warfarin>

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In Hong Kong, there are 93 registered pharmaceutical products containing miconazole, and 18 registered pharmaceutical products containing warfarin. So far, the Department of Health (DH) has not received any adverse drug reaction case resulting from coadministration of topical miconazole and warfarin. As the MHRA is currently reviewing available data for this interaction to determine whether further measures are required, DH will remain vigilant on the conclusion of the evaluation and safety updates by other overseas drug regulatory authorities for consideration of any action deemed necessary. 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)