衞生署藥物辦公室
藥物註冊及進出口管制部
香港九龍南昌街 382 號公共衞生檢測中心三樓
2319 8458
電話號碼 Tel. No.:
詢問處 Enquiries (852) 2319 8458
傳真號碼 Faxline No. (852) 2803 4962
本署檔號 OUR REF.: DH DO PRIE/7-30/15

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

29 July 2013

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

Dear Healthcare Professionals,

Safety alerts on Ketoconazole announced by US FDA, EU EMA and UK MHRA and on Metoclopramide announced by EU EMA

Your attention is drawn to the following drug safety alerts announced by US Food and Drug Administration (FDA), EU European Medicines Agency (EMA) and UK Medicines and Healthcare Products Regulatory Agency (MHRA):

1. **Ketoconaole – Potentially fatal liver injury, risk of drug interactions and adrenal gland problems**

The FDA is taking several actions related to Nizoral (ketoconazole) oral tablets, including limiting the drug's use, warning that it can cause severe liver injuries and adrenal gland problems (adrenal insufficiency) and advising that it can lead to harmful drug interactions with other medications. FDA has approved label changes and added a new Medication Guide to address these safety issues. As a result, Nizoral oral tablets should not be a first-line treatment for any fungal infection. Nizoral should be used for the treatment of certain fungal infections, known as endemic mycoses, only when alternative antifungal therapies are not available or tolerated. The topical formulations of Nizoral have not been associated with liver damage, adrenal problems, or drug interactions. FDA will continue to evaluate the safety of Nizoral tablets and will communicate with the public again if additional information becomes available.

Please refer to the following FDA's website for details:

http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm362672.htm

On top of FDA's concern, the EMA's Committee on Medicinal Products for Human Use (CHMP) recommended that the marketing authorisations of oral ketoconazole-containing medicines should be suspended throughout the EU. Doctors should no longer prescribe oral ketoconazole and should review patients' treatment options.

The CHMP assessed the available data on the risks with oral ketoconazole and concluded that, although liver injury such as hepatitis is a known side effect of antifungal medicines, the incidence and the seriousness of liver injury with oral ketoconazole were higher than with other antifungals. The CHMP was concerned that reports of liver injury occurred early after starting treatment with recommended doses, and it was not possible to identify measures to adequately reduce this risk. The CHMP also concluded that the clinical benefit of oral ketoconazole is uncertain as data on its effectiveness are limited and do not meet current standards, and alternative treatments are available.

Taking into account the increased rate of liver injury and the availability of alternative antifungal treatments, the CHMP concluded that the benefits did not outweigh the risks.

Besides, MHRA followed CHMP's decision on suspension of ketoconazole and issued a press release stating that oral ketoconazole-containing medicines should no longer be used for fungal infections.

Please refer to the following EMA and MHRA 's websites for details:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/07/news_detail_001855.jsp&mid=WC0b01ac058004d5c1

http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON297530

In Hong Kong, there are 24 oral ketoconazole-containing registered pharmaceutical products and they are all prescription-only medicines. Related news had been released by China Food and Drug Administration and Health Canada and they were posted on the Drug Office website on 1 September 2011 and 20 June 2013 respectively. We had also issued letter to you on the issue and urge to report adverse drug reactions related to oral ketoconazole previously. The matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

2. Metoclopramide - Minimising the risks of neurological and other adverse reactions by changing its use

The EMA's CHMP recommended changes to the use of metoclopramide-containing medicines in the EU after reviewing benefits and risks of these medicines in all indications and population. The recommendation includes restricting the dose and duration of use of the medicine to minimise the known risks of potentially serious neurological (brain and nerve) side effects. These medicines have been authorised separately in individual Member States of the EU, with differing licensed indications such as nausea and vomiting of various causes (for example after treatment with anticancer chemotherapy or radiotherapy, after surgery, or associated with migraine) and gastrointestinal motility disorders.

The review of metoclopramide was carried out at the request of the French medicines regulatory agency (ANSM), following continued safety concerns over side effects and concerns over efficacy. The review confirmed the well-known risks of neurological effects such as short-term extrapyramidal disorders, and tardive dyskinesia. The risk of acute (short-term) neurological effects is higher in children, although tardive dyskinesia is reported more often in the elderly, and the risk is increased at high doses or with long-term treatment. The evidence indicated that these risks outweighed the benefits of metoclopramide in conditions requiring long-term treatment. There have also been very rare cases of serious effects on the heart or circulation, particularly after injection.

The CHMP recommended that metoclopramide should only be prescribed for short-term use (up to 5 days), that it should not be used in children below 1 year of age and that in children over 1 year of age it should only be used as a second-choice treatment for the prevention of delayed nausea

and vomiting after chemotherapy and for the treatment of post-operative nausea and vomiting. In adults, it may be used for the prevention and treatment of nausea and vomiting such as that associated with chemotherapy, radiotherapy, surgery and in the management of migraine. In addition, the maximum recommended doses in adults and children should be restricted, and higher strength formulations be removed from the market.

Please refer to the following EMA's website for details:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/07/news_detail_001854.jsp&mid=WC0b01ac058004d5c1

In Hong Kong, there are 32 metocopramide-containing registered pharmaceutical products and they are all prescription-only medicines. In view of the recommendations from EMA, 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 the drugs to the Pharmacovigilance Unit of Department of Health (tel. no.: 2319 2920, fax: 2186 9845 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 drug safety digest of drug safety news and information issued by Drug Office.

Yours faithfully,

(Ms. Pamela LI)
for Assistant Director (Drug)