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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

BY FAX

19 September 2016

Dr. Donald LI
President
Hong Kong Academy of Medicine
(Fax Number: 2505 5577)

Dear Dr. LI,

Levonorgestrel-containing emergency hormonal contraception: advice on interactions with hepatic enzyme inducers and contraceptive efficacy

Your attention is drawn to the Medicines and Healthcare products Regulatory Agency's (MHRA) announcement regarding interactions of levonorgestrel-containing emergency hormonal contraception with medicines or herbal remedies that induce CYP3A4 enzymes reduce blood levels of levonorgestrel, which may reduce emergency contraceptive efficacy.

Levonorgestrel-containing emergency contraception is used to prevent unintended pregnancy when taken within 72 hours (3 days) of unprotected intercourse or failure of a contraceptive method. The sooner it is taken after having unprotected sex, the more effective it will be.

Concomitant use of liver enzyme inducers—mainly inducers of CYP3A4 enzymes—increases the metabolism of levonorgestrel. Examples of enzyme inducers that reduce plasma levonorgestrel levels are some medicines used to treat:

- epilepsy (eg, barbiturates, primidone, phenytoin, carbamazepine)
- tuberculosis (eg, rifampicin, rifabutin)
- HIV (eg, ritonavir, efavirenz)
- fungal infections (eg, griseofulvin)

Concomitant administration of the antiretroviral efavirenz (used to treat HIV) reduces plasma levels (AUC) of levonorgestrel by around 50%. Data are not available for all CYP3A4 enzyme inducers; however, studies of levonorgestrel-containing combined hormonal contraceptives show that other hepatic enzyme-inducing medicines or herbal medicines may produce similar reductions in plasma levels. These contraceptive products already contain advice on additional or alternative methods of contraception.

Herbal remedies that contain St John's wort (Hypericum perforatum) also reduce levonorgestrel levels.

Elevated levels of CYP3A4 enzymes can persist for up to 4 weeks after cessation of the enzyme-inducing medicine. This decrease in plasma levonorgestrel may reduce contraceptive efficacy of levonorgestrel-containing emergency hormonal contraceptives.

Exposure during pregnancy to some of the enzyme-inducing medicines listed above has been associated with an increased risk of birth defects. It is therefore important to provide advice on highly effective forms of regular contraception for women who take these medicines, and to exclude pregnancy after use of levonorgestrel-containing emergency contraception.

The updated MHRA advice for healthcare professionals is as follows:

- women seeking emergency contraception who have used cytochrome P450 3A4 (CYP3A4) enzyme inducers within the last 4 weeks, should:
  - preferably use a non-hormonal emergency contraceptive—ie, a copper intrauterine device
  - if this is not an option, double the usual dose of levonorgestrel from 1.5 milligrams to 3 milligrams (ie, 2 packs)
- for these women:
  - provide advice on highly effective ongoing contraception that is not affected by hepatic enzyme-inducing drugs
  - advise them to have a pregnancy test to exclude pregnancy after use of levonorgestrel-containing emergency contraception
  - advise them to seek prompt medical advice if they do become pregnant

This updated advice is in line with existing guidance from UK experts in sexual and reproductive health, and applies to both prescription and non-prescription supply which will help ensure that women receive consistent advice. Product information for healthcare professionals and women and the outer packaging for levonorgestrel emergency contraception are being updated with this advice.

Please refer to the MHRA's website for details:

https://www.gov.uk/drug-safety-update/levonorgestrel-containing-emergency-hormonal-contraception-advice-on-interactions-with-hepatic-enzyme-inducers-and-contraceptive-efficacy

In Hong Kong, there are 37 registered pharmaceutical products containing levonorgestrel, of which 30 products are prescription only medicines, including 29 products containing levonorgestrel 0.75mg/tablet or 1.5mg /tablet and 1 intrauterine device; while 7 products are over-the-counter medicines containing levonorgestrel 0.15mg or below. So far, the Department of Health (DH) has not received any adverse drug reaction report related to levonorgestrel. In view of the above MHRA announcement, the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board. Healthcare professionals are advised to take note of the above advice when providing relevant treatment and to balance the risk of possible drug interactions or 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 sincerely,

(Joseph LEE)
for Assistant Director (Drug)