



D r u g N e w s

藥 物 情 報

Issue Number 83

This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in September 2016 with relevant information update before publish. For the latest news and information, please refer to public announcements or the website of the Drug Office of the Department of Health (<http://www.drugoffice.gov.hk>).

Safety Update

Canada: Health Canada reinforces the importance of preventing pregnancy while taking the acne drug isotretinoin to avoid birth defects

On 7 September 2016, Health Canada is reminding Canadians of the serious risk of birth defects associated with taking the prescription acne drug isotretinoin while pregnant. Health professionals and women who are using, or considering using this drug are reminded of the importance of not getting pregnant while taking this treatment.

Isotretinoin, available under the brand names Accutane, Clarus and Epuris in Canada, is used to treat severe acne when other therapies have not worked. It has been available in Canada for more than 30 years. The reminder comes in light of a recent study commissioned by Health Canada. Health Canada commissioned the study as part of ongoing work to evaluate the risk-management measures currently in place for isotretinoin. The study identified continued reports of pregnancy among patients using isotretinoin, despite the comprehensive risk management measures in place.

There is a known, high risk of birth defects if a woman gets pregnant while taking isotretinoin. This includes malformation of the limbs, head, face, heart and central nervous system of a fetus. To address this risk, Canada, like other countries, has instituted a pregnancy prevention program. Specifically, the program requires patients' written consent, two negative pregnancy tests before starting treatment, monthly tests during treatment and one month after stopping, and the use of two reliable methods of birth control through this period.

Products are prominently labelled to warn of the risk of birth defects and the importance of actively preventing pregnancy. In addition, manufacturers provide comprehensive patient screening and monitoring tools and advice, reminders to health professionals, educational materials, which both prescribers and patients are strongly encouraged to use, and websites providing pregnancy prevention materials.

Health Canada continues to assess what additional measures may be needed. Canadians will be informed of any new steps to improve the safe use of isotretinoin.

Patients are advised that if they are a female of childbearing age and are planning to use isotretinoin, they and their health care professional should carefully adhere to the pregnancy prevention program. It is essential to use two reliable methods of birth control for at least one month before starting therapy, during therapy, and for at least one month after stopping isotretinoin use. If they do get pregnant while taking isotretinoin, stop taking the drug immediately and consult their health professional.

Healthcare professionals are advised of the following:

- Isotretinoin should be reserved for patients with severe acne who have not responded to conventional first-line acne therapies.
- Ensure that all patients using isotretinoin (male and female) sign an informed consent form.
- Ensure that females of childbearing potential fulfill the "Conditions of Use" listed in isotretinoin product monographs.

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- Apply all aspects of the isotretinoin pregnancy prevention program when prescribing isotretinoin. Product monographs provide instructions for obtaining these materials either in hard copy or online.

In Hong Kong, there are 12 registered pharmaceutical products containing isotretinoin, and are prescription only medicines. Currently, there are registration requirements that a patient information leaflet, in both Chinese and English, should be provided in each registered pharmaceutical product containing isotretinoin, with warnings on the teratogenic side effects of isotretinoin. As on 9 December 2016, the Department of Health (DH) has received one adverse drug reaction (ADR) case related to isotretinoin and miscarriage. As Health Canada will continue to assess the additional measures to improve the safe use of isotretinoin, DH will remain vigilant on the conclusion of the review and any safety updates on isotretinoin by other overseas drug regulatory authorities.

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

On 15 September 2016, the Medicines and Healthcare products Regulatory Agency (MHRA) advised that medicines or herbal remedies that induce cytochrome P450 3A4 (CYP3A4) enzymes reduce blood levels of levonorgestrel, may reduce emergency contraceptive efficacy.

The MHRA issued updated advice for healthcare professionals:

- women seeking emergency contraception who have used 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 (United Kingdom) 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 in UK are being updated with this advice.

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. In the UK, levonorgestrel-containing emergency contraception is available with or without a prescription as a single 1500 microgram tablet, or on prescription as two 750 microgram tablets taken as a single dose.

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.

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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.

In Hong Kong, there are 37 registered pharmaceutical products containing levonorgestrel, of which 30 products are prescription only medicines, including 28 products containing levonorgestrel either 0.75mg or 1.5mg per tablet for emergency contraception and 1 product as intrauterine contraceptive device; while 7 products are over-the-counter medicines containing levonorgestrel 0.15mg or below per tablet for contraceptive purposes only. As on 9 December 2016, DH has not received any ADR report related to levonorgestrel. In view of the MHRA announcement, DH issued a letter to inform local healthcare professionals on the above risk of drug interactions on 19 September 2016, and the issue will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

UK: Freshers warned to be smart and avoid Modafinil

On 26 September 2016, freshers and university students are being warned of the possible dangers to their health from taking powerful prescription medicines to get higher marks as a new university year begins.

The MHRA research showed 14% of those sampled were likely to buy so-called 'smart drugs' within the next year. The misuse of prescription only medicines such as Modafinil and Ritalin remains prevalent despite repeated warnings

against self-medication. Possible side effects of using 'cognitive enhancers' include risk of dependence, cardiovascular problems and psychosis.

MHRA has recently launched the FakeMeds campaign aimed at young adults and highlighting the pitfalls of buying medicines online. So far this year, MHRA has shut down nearly 5,000 websites selling fake or unlicensed medicines.

MHRA advised that modafinil is licensed for specific medical conditions – not for use as a 'boost' during exams. Freshers and university students should not put their health at risk by self-medication as it could have serious side effects.

In Hong Kong, there are 11 registered pharmaceutical products containing methylphenidate which are prescription only medicines and dangerous drugs including 3 Ritalin products, and no registered pharmaceutical product containing modafinil. Members of the public should not purchase pharmaceutical products from doubtful sources, including from Internet sites, as the safety, quality and efficacy of the products cannot be guaranteed.

DH endorsed batch recall of Nimotop Tablets 30mg (HK-28974)

On 7 September 2016, DH endorsed a licensed drug wholesaler, Bayer Healthcare Limited (Bayer), to recall four batches (batch numbers: 404514, 239414-H1, 033315 and 507815) of Nimotop Tablets 30mg (HK-28974) from the market because the package insert of the product does not match with the registered version.

DH received notification from Bayer that, during its routine inspection, the above-mentioned product was found bearing a package insert without a warning statement rendering the product unregistered. The warning statement was: "In patients with unstable angina or within the first 4 weeks after acute myocardial infarction, physicians should consider the potential risk (e.g. reduced coronary artery perfusion and myocardial ischemia) versus the benefit (e.g. improvement of brain perfusion)". Since the supply of unregistered pharmaceutical product is a contravention of the Pharmacy and Poisons Regulations (Cap. 138A), Bayer voluntarily recalled the affected batches from the market.

The above product, containing Nimodipine, is a prescription only medicine used for the prevention of ischaemic neurologic deficits following aneurysmal subarachnoid haemorrhage.

According to Bayer, the affected batches of the product have been supplied to Hospital Authority, private hospitals, private doctors and community pharmacies.

As on 9 December 2016, DH has not received any ADR report related to the above product. A notice was posted on the Drug Office website on 7 September 2016 to alert the public of the product recall.

DH endorsed recall of Xuzulex Nasal Spray (OSCO) 0.1% (HK-59553)

On 19 September 2016, DH endorsed a licenced drug wholesaler, Wilson Trading Co. Ltd. (Wilson), to recall all batches of Xuzulex Nasal Spray (OSCO) 0.1% (HK-59553) from the market because the label and package insert of the product do not

match with the registered version.

During DH market surveillance, sample of the above product was collected for analysis and examination. DH found that the label and package insert of the product were different from the registered version, rendering the product unregistered. Since the supply of unregistered pharmaceutical product is a contravention of the Pharmacy and Poisons Regulations (Cap. 138A), Wilson voluntarily recalled the product from the market.

The above product, containing xylometazoline, is an over-the-counter medicine used for the relief of nasal congestion. According to Wilson, the product has been supplied to local pharmacies.

As on 9 December 2016, DH has not received any ADR report related to the affected product. A notice was posted on the Drug Office website on 19 September 2016 to alert the public of the product recall.

A product containing any western drug ingredient must be registered under the Pharmacy and Poisons Ordinance before it can be sold in Hong Kong. Part 1 poisons should be sold at registered pharmacies under the supervision of registered pharmacists. Illegal sale or possession of Part 1 poisons and unregistered pharmaceutical products are offences under the Pharmacy and Poisons Ordinance (Cap 138). The maximum penalty is a fine of \$100,000 and two years' imprisonment for each offence. Antibiotics can only be supplied at registered pharmacies by registered pharmacists or under their supervision and upon a doctor's prescription. They should only be used under the advice of a doctor. Illegal sale or possession of antibiotics are offences under the Antibiotics Ordinance (Cap 137) and the maximum penalty is a \$30,000 fine and one year's imprisonment for each offence.

Useful Contact

Drug Complaint:

Tel: 2572 2068

Fax: 3904 1224

E-mail: pharmgeneral@dh.gov.hk

Adverse Drug Reaction (ADR) Reporting:

Tel: 2319 2920

Fax: 2319 6319

E-mail: adr@dh.gov.hk

Link: <http://www.drugoffice.gov.hk/adr.html>

Post: *Pharmacovigilance Unit,
Drug Office, Department of Health,
Rm 1856, 18/F, Wu Chung House,
213 Queen's Road East,
Wan Chai, Hong Kong*

The purpose of Drug News is to provide healthcare professionals with a summary of local and overseas drug safety news released. Healthcare professionals are advised to keep update with the information and provide corresponding advice or therapeutic measure to patients and public.