Drug News
藥 物 情 報

Issue Number 84

This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in October 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: FASLODEX (fulvestrant) - risk of unnecessary therapy modification due to falsely elevated estradiol levels

On 18 October 2016, Health Canada advised that medical and scientific literature as well as post marketing reports suggest that fulvestrant can cross react with estradiol (E2) immunoassays due to structural similarity with estradiol. The false E2 positive assays may lead to misinterpretation of the menopausal status of women therefore putting patients at risk for unnecessary surgery or endocrine therapy modification.

FASLODEX® (fulvestrant) 50 mg/mL injection is indicated in Canada for the hormonal treatment of locally advanced or metastatic breast cancer in postmenopausal women, regardless of age, who have disease progression following prior anti-estrogen therapy. By stopping some of the actions of estrogen, FASLODEX reduces the amount that is in the body, which has an effect in reducing breast cancer tumour growth.

Rare international cases of false positive increased estradiol levels have been reported in patients receiving FASLODEX, resulting in unnecessary surgery being performed. It could also potentially result in modification of endocrine therapy being initiated. The measurement of low estradiol levels is challenging because of the lack of standardization at low levels in postmenopausal women and the variation in sensitivity/specificity among different immunoassays. Studies suggest that direct immunoassay kits from different manufacturers provide different results and are not always reliable to measure estradiol levels in patients receiving fulvestrant therapy. It is therefore important to recognize the limitations of individual estradiol tests and choose an alternative test method (such as liquid chromatography-mass spectrometry).

Consumers are advised that blood tests to check levels of estradiol (a hormone) may be used during FASLODEX treatment to confirm menopausal status as, with breast cancer patients, this can sometimes change. There have been reports that FASLODEX can interfere with estradiol blood tests and produce incorrect results. Incorrect test results could potentially lead to beneficial therapy being changed or stopped unnecessarily. In rare cases, misinterpreting a patient as premenopausal can lead to unnecessary surgery.

Healthcare professionals are advised that when requesting blood tests that include estradiol, indicate if the patient is on FASLODEX. Caution should be exercised when performing antibody-based estradiol assays for patients taking FASLODEX. The need to carry out a review of the previously reported test results should be considered. Alternative methods such as liquid chromatography-mass spectrometry should be considered.

Healthcare professionals should continue to use estradiol immunoassays for patients not on FASLODEX.

Health Canada in collaboration with AstraZeneca Canada Inc. has updated the FASLODEX Canadian Product Monograph advising of this safety risk.

In Hong Kong, Faslodex Soln for Inj 250mg/5ml (Pre-filled Syringe) (HK-57103) is a

pharmaceutical product registered by AstraZeneca Hong Kong Ltd, and is a prescription only medicine. As on 11 January 2017, the Department of Health (DH) has not received any adverse drug reaction (ADR) report related to the product. In view of the Health Canada announcement, DH issued letters to inform local healthcare professionals to draw their attention on 19 October 2016, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board (the Registration Committee). DH will remain vigilant on any safety update on the product by other overseas drug regulatory authorities.

UK: Etoricoxib (Arcoxia): revised dose recommendation for rheumatoid arthritis and ankylosing spondylitis

On 17 October 2016, the Medicines and Healthcare products Regulatory Agency (MHRA) advised that prescribing information of etoricoxib (Arcoxia) has been updated to introduce a lower recommended dose of 60 mg daily for patients with rheumatoid arthritis or ankylosing spondylitis.

Etoricoxib belongs to the selective COX-2 inhibitor class of drugs and may be associated with an increased risk of coronary and cerebrovascular thrombotic events, heart failure, hypertension, and oedema (compared with placebo and some non-steroidal anti-inflammatory drugs). Other important risks to consider with etoricoxib are effects on the gastrointestinal system, particularly those of perforation, ulceration, or bleeding.

Following an EU-wide review in 2008 of the benefits and risks of etoricoxib, the marketing authorisation holder was required to do clinical trials to assess the efficacy and safety of etoricoxib 60 mg once daily for the treatment of rheumatoid arthritis and ankylosing spondylitis including comparison with etoricoxib 90 mg.

From these trials, there is evidence that the 60-mg dose is effective in rheumatoid arthritis and ankylosing spondylitis. However, for some patients, the 90-mg dose will be more efficacious, although prediction of which patients might benefit from the higher dose is not possible.

Therefore, the recommended starting dose for treatment of rheumatoid arthritis or ankylosing spondylitis has been reduced to 60 mg once daily, with the option to increase to a maximum of 90 mg once daily if necessary.

The MHRA advised healthcare professionals of the following:

- the cardiovascular and other important risks of etoricoxib (Arcoxia) may increase with dose and duration of exposure. Therefore, the lowest effective daily dose should be used, and the need for treatment should be regularly reassessed
- the recommended dose is 60 mg once daily
- in patients with insufficient relief from symptoms, an increased dose of 90 mg once daily may improve efficacy
- once the patient is clinically stabilised, down-titration to 60 mg once daily may be appropriate
- in the absence of therapeutic benefit, other treatment options should be considered

In Hong Kong, Arcoxia Tab 30mg (HK-57452), 60mg (HK-51227), 90mg (HK-51225) and 120mg (HK-51226) are pharmaceutical products registered by Merck Sharp & Dohme (Asia) Ltd (MSD), and are prescription only medicines. As on 11 January 2017, DH has received five cases of ADR in connection with etoricoxib, and the cases involved gastrointestinal haemorrhage, rash, aphothous stomatitis, non-specific lips swelling, swelling of limbs, blister, mouth swelling and hypersensitivity. MSD has submitted application to update the package insert of the products to reduce the recommended dose which is in line with the MHRA announcement, and the application is under evaluation. DH will remain vigilant on any safety update on etoricoxib by other overseas drug regulatory authorities.

US: Testosterone and other anabolic androgenic steroids (AAS): FDA statement - Risks associated with abuse and dependence

On 25 October 2016, the US Food and Drug Administration (FDA) approved class-wide labeling changes for all prescription testosterone products, adding a new Warning and updating the Abuse and Dependence section to include new

safety information from published literature and case reports regarding the risks associated with abuse and dependence of testosterone and other AAS.

Prescription testosterone products are FDA-approved as hormone replacement therapy for men who have low testosterone due to certain medical conditions. Examples of these conditions include failure of the testicles to produce testosterone because of genetic problems, or damage to the testicles from chemotherapy or infection.

The Anabolic Steroids Control Act of 1990 placed AAS, including testosterone, in Schedule III of the Controlled Substances Act. Testosterone and other AAS are abused by adults and adolescents, including athletes and body builders. Abuse of testosterone, usually at doses higher than those typically prescribed and usually in conjunction with other AAS, is associated with serious safety risks affecting the heart, brain, liver, mental health, and endocrine system. Reported serious adverse outcomes include heart attack, heart failure, stroke, depression, hostility, aggression, liver toxicity, and male infertility. Individuals abusing high doses of testosterone have also reported withdrawal symptoms, such as depression, fatigue, irritability, loss of appetite, decreased libido, and insomnia.

The FDA alerts prescribers to the followings labelling changes:

- New Warning on the abuse potential of testosterone and the serious adverse outcomes, especially those related to heart and mental health that have been reported in association with testosterone/AAS abuse.
- Revised labeling of all testosterone products to include information in the Abuse and Dependence section about adverse outcomes reported in association with abuse and dependence of testosterone/AAS.
- Warning and Precautions section advising prescribers of the importance of measuring serum testosterone concentration if abuse is suspected.

In Hong Kong, there are six registered pharmaceutical products containing testosterone, and one registered pharmaceutical product containing methyltestosterone, which are all prescription only medicines. News on the cardiovascular risk of testosterone was previously issued by EMA, US FDA, Health Canada and Singapore HSA, and was reported in the Drug News Issue No. 52, 57, 60, 65 and 72. DH issued letters to inform local healthcare professionals to draw their attention on 20 June 2014, 16 July 2014 and 13 October 2014. The matter was discussed by the Registration Committee on 17 February 2015. The Registration Committee noted that DH had informed the relevant registration certificate holders to include the warnings on cardiovascular risk on their testosterone products. As on 11 January 2017, DH has received one case of ADR related to testosterone and associated with non-specific lips swelling and breath shortness. In view of the above US FDA announcement on the risk of abuse and dependence with anabolic androgenic steroids including testosterone, DH issued letters to inform local healthcare professionals to draw their attention on 26 October 2016, and the matter will be discussed by the Registration Committee.

Canada: SOLIRIS (eculizumab) - Increased risk of hemolysis or low hemoglobin with serogroup B meningococcal vaccination

On 25 October 2016, Health Canada advised that an increased risk of hemolysis or low hemoglobin has been observed when patients already being treated with SOLIRIS (eculizumab) were vaccinated against serogroup B meningococcal infection with Bexsero.

During a safety review of Bexsero, a vaccine used to protect against Neisseria meningitides serogroup B, Health Canada found more reports of serious adverse reactions with Bexsero in patients with complement mediated diseases (such as paroxysmal nocturnal hemoglobinuria [PNH] and atypical haemolytic uremic syndrome [atypical HUS]) who were being treated with SOLIRIS (a complement inhibitor), than in other patients vaccinated with Bexsero. Bexsero was marketed in Canada in 2014, which is 5 years after SOLIRIS (marketed since 2009). A further review of the reports with Bexsero in patients already being treated with SOLIRIS concluded that there was an increased risk of low hemoglobin, including anemia, or hemolysis. The risk was highest in patients receiving Bexsero vaccine when their predicted systemic SOLIRIS concentrations were relatively low.

SOLIRIS is a complement inhibitor indicated for the treatment of patients with PNH to reduce hemolysis, and for the treatment of patients with atypical HUS to reduce complement-mediated thrombotic microangiopathy (TMA).

SOLIRIS blocks terminal complement activation; therefore patients may have increased susceptibility to infections, particularly meningococcal disease caused by *Neisseria meningitidis*. Consequently, all patients must be vaccinated against meningococcal infections prior to, or at the time of, initiating SOLIRIS, unless the risks of delaying SOLIRIS therapy outweigh the risks of developing a meningococcal infection.

Vaccination, particularly with a vaccine against serogroup B meningococcal infection, in patients already being treated with SOLIRIS, may further activate complement. As a result, patients with complement-mediated diseases, including PNH and atypical HUS, may experience increased symptoms of their underlying disease, such as hemolysis (PNH) or thrombotic microangiopathy (TMA) complications (atypical HUS). To minimize this risk, it is recommended to vaccinate patients who are already being treated with SOLIRIS only when the underlying complement-mediated disease is clinically controlled and within one week of SOLIRIS infusion, when systemic SOLIRIS concentrations are considered to be relatively high.

Healthcare professionals are advised that careful consideration should be given to the timing of meningococcal vaccination relative to the administration of SOLIRIS in patients who initiate therapy and also for those receiving maintenance therapy.

- For patients stabilized on SOLIRIS and receiving maintenance therapy, and for whom additional vaccination is warranted, vaccination is only recommended when the underlying complement-mediated disease is clinically controlled with SOLIRIS, and within one week following SOLIRIS infusion, when systemic SOLIRIS concentrations are considered to be relatively high.
- All patients taking SOLIRIS must be vaccinated with a meningococcal vaccine prior to, or at the time of, initiating SOLIRIS.
- Patients who start on SOLIRIS treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics for 2 weeks after they are vaccinated.

Healthcare professionals are reminded to provide their patients with relevant information to increase their awareness of potential serious infections and their signs and symptoms. All patients must be monitored for early signs of meningococcal infections, evaluated immediately if infection is suspected, and treated with antibiotics, if necessary.

In Hong Kong, Soliris Concentrate for Solution for Infusion 300mg/30ml (HK-61188) containing eculizumab is a pharmaceutical product registered by DKSH Hong Kong Limited which is a prescription only medicine; and there are four registered meningococcal vaccines, namely Meningococcal A+C Polysaccharide Vaccine (HK-36398), Mencevax ACWY Vaccine (HK-48475), Menactra Vaccine (HK-60659) and Nimenrix Vaccine (HK-62095) which are prescription only medicines; while Bexsero is not a registered meningococcal vaccine. As on 11 January 2017, DH has received six cases of ADR in connection with eculizumab, but none of them was associated with haemolysis after meningococcal vaccination. In view of the Health Canada announcement, DH issued letters to inform local healthcare professionals to draw their attention on 26 October 2016, and the matter will be discussed by the Registration Committee.

Drug Recall

DH endorsed recall of Tanatril Tablets 5mg (HK-51394)

On 6 October 2016, DH endorsed a licensed drug wholesaler, Primal Chemical Co., Ltd (Primal), to recall all batches of Tanatril Tablets 5mg (HK-51394) due to a potential quality issue.

DH received notification from Primal that the manufacturer of the product in Indonesia is recalling the product because some of the product samples failed the test for related substances during its stability study. According to the assessment of the manufacturer, the risk posed by the issue is minimal and the recall is a precautionary measure.

Tanatril tablet 5mg, containing imidapril, is a prescription only medicine used for the treatment of hypertension. According to Primal, the product has been supplied to private hospitals, doctors and local pharmacies.

As on 11 January 2017, DH has not received any ADR report related to the above product. A notice was posted on the Drug Office website on 6 October 2016 to alert the public of the product recall.

Drug Incident

Woman arrested for suspected illegal sale of slimming product with undeclared drug ingredient

On 12 October 2016, a woman aged 27 was arrested in a joint operation by DH and the Police for the suspected illegal sale of a slimming product called "ele Slim Shot" that was suspected to contain an undeclared Western drug ingredient.

During DH's market surveillance, a sample of the above product was purchased from an Internet seller for analysis. Testing results of the Government Laboratory showed that the sample contained a Part 1 poison, orlistat. The Police arrested the seller for the suspected illegal sale of an unregistered pharmaceutical product and Part 1 poison in the operation.

Orlistat is a Part 1 poison used for the treatment of obesity. Its side-effects include faecal urgency, fatty stool, increased frequency of defaecation, faecal incontinence, headache and abdominal pain. Severe liver injuries may also be induced.

A notice was posted on the Drug Office website on 12 October 2016 to alert the public of the drug incident.

DH urges public not to consume slimming product with undeclared banned drug ingredient

On 13 October 2016, DH appealed to the public not to buy or consume a slimming product labelled in Japanese (photographs are available on Drug Office website) as it was found to contain an undeclared and banned drug ingredient which may be dangerous to health.

Acting upon intelligence, a sample of the above product was earlier purchased from an Internet seller for analysis. Test results from the Government Laboratory revealed that the sample contained sibutramine.

Sibutramine is a Part 1 poison and was once used as an appetite suppressant. Since November 2010, products containing sibutramine have been banned in Hong Kong for their increased cardiovascular risk.

Weight control should be achieved through a balanced diet and appropriate exercises. The public should consult healthcare professionals before using any medication for weight control.

A notice was posted on the Drug Office website on 13 October 2016 to alert the public of the drug incident.

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.

All registered pharmaceutical products should carry a Hong Kong registration number on the package in the format of "HK-XXXXX". The products mentioned in the above incidents were not registered pharmaceutical products under the Ordinance in Hong Kong. Their safety, quality and efficacy cannot be guaranteed. Members of the public were exhorted not to use products of unknown or doubtful composition. They should stop using the aforementioned products immediately if they had them in their possession and to consult healthcare professionals if they felt unwell after taking the products. The products should be destroyed or disposed properly, or submitted to the Department's Drug Office during office hours.

Details of ALL registered pharmaceutical products can be found in the Drug Office website at http://www.drugoffice.gov.hk/eps/do/en/healthcare_providers/news_informations/reListRPP_index.html. In particular, for newly registered medicines in the past year, they can be found at http://www.drugoffice.gov.hk/eps/drug/newsNRM60/en/pharmaceutical_trade?pageNoRequested=1.

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,
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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.