



This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in May 2013 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

US: FDA limits duration and usage of Samsca (Tolvaptan) due to possible liver injury leading to organ transplant or death

It was noted from the website of the Food and Drug Administration (FDA) of the United States (US) on 2 May 2013 that FDA had determined the drug Samsca (tolvaptan) should not be used for longer than 30 days and should not be used in patients with underlying liver disease because it can cause liver injury, potentially requiring liver transplant or death. An increased risk of liver injury was observed in recent large clinical trials evaluating Samsca for a new use in patients with autosomal dominant polycystic kidney disease (ADPKD). FDA had worked with the manufacturer to revise the Samsca drug label to include these new limitations. Patients should be aware that Samsca may cause liver problems, including life-threatening liver failure, and should contact their healthcare professionals to discuss any questions or concerns about Samsca.

In Hong Kong, Samsca Tablet 15mg (HK-59910) and 30mg (HK-59911) are registered by Otsuka Pharmaceutical (HK) Ltd. and are prescription only medicines. They are indicated for the treatment of clinically significant hypervolaemic and euvolaemic hyponatraemia, including patients with heart failure, cirrhosis and Syndrome of Inappropriate Antidiuretic Hormone (SIADH). A letter to healthcare professionals was issued on 28 January 2013, and the Pharmacy and Poisons (Registration of Pharmaceutical Products and Substances: Certificate of Clinical Trial/Medicine Test) Committee (the Registration Committee) of the Pharmacy and Poisons Board had discussed the matter in February 2013 and its decision was reported in Drug News Issue No. 39. In view of

the latest FDA's recommendations, another letter was issued on 2 May 2013 and the Registration Committee decided at its latest meeting that tolvaptan-containing products should also include the appropriate safety information, such as examples given as below:

- A. Under "Indication": of the indication for use in patients with cirrhosis.
- B. Under "Dosage": do not administer tolvaptan for more than 30 days to minimize the risk of liver injury.
- C. Under "Warnings and Precautions":
 - i. tolvaptan can cause serious and potentially fatal liver injury. In a placebo-controlled and open label extension study of chronically administered tolvaptan in patients with autosomal dominant polycystic kidney disease, cases of serious liver injury attributed to tolvaptan were observed. An increased incidence of ALT greater than three times the upper limit of normal was associated with tolvaptan (42/958 or 4.4%) compared to placebo (5/484 or 1.0%). Cases of serious liver injury were generally observed starting 3 months after initiation of tolvaptan although elevations of ALT occurred prior to 3 months;
 - ii. patients with symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice should discontinue treatment with tolvaptan; and
 - iii. limit duration of therapy with tolvaptan to 30 days. Avoid use in patients with underlying liver disease, including cirrhosis, because the ability to recover from liver injury may be impaired.

Singapore: Recommendations for HLA-B*1502 genotype testing prior to initiation of carbamazepine in new patients

It was noted from the website of the Health Sciences Authority (HSA) of Singapore on 2 May 2013 that the Ministry of Health informed healthcare professionals the genotyping for the HLA-B*1502 allele prior to the initiation of carbamazepine therapy in new patients of Asian ancestry is now considered the standard of care. HSA will strengthen the local package inserts for this drug product to highly recommend HLA-B*1502 genotyping test.

In Hong Kong, there are 12 registered pharmaceutical products containing carbamazepine. They are all prescription only medicines indicated for the treatment of epilepsy and conditions such as trigeminal neuralgia and bipolar disorders. A letter to healthcare professionals was issued on 7 May 2008 regarding carbamazepine can induce Steven Johnson syndrome and toxic epidermal necrolysis, especially in patients with a particular Human Leucocyte Antigen (HLA) allele HLA-B*1502. The matter was discussed by the Registration Committee of the Pharmacy Poisons Board in 2008, and the Committee decided that carbamazepine-containing products should include the appropriate warning on the sales pack label and/or package insert. In view of HSA's action, another letter was issued on 2 May 2013. The Department of Health (DH) will keep vigilance on any safety updates of the drug and actions taken by other overseas regulatory authorities for consideration of any action deemed necessary.

Singapore: Intramuscular medroxyprogesterone and injection site necrosis and atrophy

It was noted from HSA website on 6 May 2013 that healthcare professionals were informed on overseas reports of injection site necrosis and atrophy associated with the use of intramuscular (IM) medroxyprogesterone. In Singapore, medroxyprogesterone acetate is available as an IM injection under the brand name Depo-Provera (Pfizer Pte. Ltd). As of 31 July 2012, a total of 103 medically confirmed global cases of injection site reactions associated with the IM route of administration of medroxyprogesterone were

reported to the company. Of these reports, 30.1% were serious and described events such as injection site atrophy, atrophy, skin atrophy, lipoatrophy, injection site necrosis, necrosis, fat necrosis, injection site ulcer, and muscle necrosis. In 44.7% of the cases, there were insufficient information (e.g., site of reaction, dates of onset) to allow a meaningful medical assessment. In 20.4% of the cases, IM medroxyprogesterone injection were reported to be administered at the thigh region instead of the recommended deltoid or gluteal region. There were also 25.2% of cases where the role of IM medroxyprogesterone in the development of injection site necrosis and atrophy could not be ruled out. HSA had not received any reports on injection site reactions associated with the use of IM medroxyprogesterone. HSA was working with the company to further strengthen the warnings in the local package insert for Depo-Provera to include injection site necrosis and skin atrophy as potential injection site reactions. Healthcare professionals are reminded to take into consideration the above safety updates when prescribing IM medroxyprogesterone.

In Hong Kong, three intramuscular injectable pharmaceutical products containing medroxyprogesterone are registered, namely Depo-Provera Contraceptive Inj 150mg/ml (HK-43794), Cyclofem Inj (HK-54438), and Depogestin I Suspension for Inj 150mg (HK-60455). They are prescription only medicines indicated for contraceptive use. DH had not received any related adverse reports in connection with the drug. In view of HSA's announcement, a letter to healthcare professionals was issued on 6 May 2013, and the matter will be discussed in the meeting of the Registration Committee of the Pharmacy and Poisons Board.

Singapore: Levothyroxine and potential risk of fractures

It was noted from HSA website on 6 May 2013 that an increase in the risk of fractures associated with the use of levothyroxine had been observed in a recent study. Outcomes of the study found that current and recent past levothyroxine use were associated with a significant increased risk of any fractures when compared to remote levothyroxine use. Among current levothyroxine users, a higher risk of any fractures was observed for high

(>0.093mg/day) and medium (0.044 to 0.093mg/day) cumulative doses of levothyroxine when compared to low (<0.044mg/day) cumulative doses. Additionally, healthcare professionals should be aware that long-term suppressive doses of levothyroxine therapy has been associated with increased bone resorption and reduced bone mineral density, especially in post-menopausal women. There is limited information on the effect of levothyroxine on bone mineral density in the local package inserts of levothyroxine products and they will be further strengthened with this safety information. Healthcare professionals are advised to take into consideration this safety information when prescribing levothyroxine to their patients and to prescribe the minimum dose necessary to achieve the desired clinical and biochemical response.

In Hong Kong, there are nine registered pharmaceutical products containing levothyroxine and all are prescription only medicines. They are indicated as replacement therapy in the treatment of thyroid hormone deficiency. DH had not received any related adverse reports in connection with the drug. In view of HSA's announcement, a letter to healthcare professionals was issued on 6 May 2013, and the matter will be discussed in the meeting of the Registration Committee of the Pharmacy and Poisons Board.

Singapore: Rivaroxaban (Xarelto®) and reports of lack of efficacy in orthopaedic surgery indication

It was noted from HSA website on 6 May 2013 that a review of the adverse drug reaction (ADR) reports received by the Netherlands Pharmacovigilance Centre, Lareb, raised a possible signal of lack of efficacy with Xarelto® for the prevention of venous thromboembolism in adult patients undergoing elective hip or knee replacement surgery. As of March 2012, Lareb had received 48 ADR reports related to the use of rivaroxaban. Of these, 31 were reported as serious and the most frequently reported serious ADRs were bleeding events. There were also eight reports of pulmonary embolism (PE) associated with the use of rivaroxaban, which indicated a possible lack of efficacy in certain patients. The reports from HSA's ADR database had not shown a similar trend for inefficacy and the safety signal observed in the

Netherlands could be due to stimulated reporting, i.e. reporters were more likely to report possible adverse events of new drugs as compared to older drugs. HSA continues to monitor for reports of PE associated with rivaroxaban although there was no report of PE in Singapore. Healthcare professionals are advised to monitor their patients for possible lack of efficacy.

In Hong Kong, there are three registered pharmaceutical products containing rivaroxaban, namely Xarelto Tab 10mg (HK-57861), 15mg (HK-61396) and 20mg (HK-61395). They are prescription only medicines registered by Bayer Healthcare Ltd. Xarelto Tab 10mg is indicated for the prevention of venous thromboembolism in adult patients undergoing elective hip or knee replacement surgery; whereas Xarelto Tab 15mg and 20mg are indicated for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation and treatment of deep vein thrombosis. DH had received one adverse report concerning suspected intracranial hemorrhage in connection with rivaroxaban, and no cases on lack of efficacy were received. In view of HSA's announcement, a letter to inform healthcare professionals was issued on 6 May 2013. DH will keep vigilance on any safety updates of the drug and actions taken by other overseas regulatory authorities for consideration of any action deemed necessary.

US: Valproate and related products are contraindicated for pregnant women for prevention of migraine headaches

On 6 May 2013, FDA advised healthcare professionals that the anti-seizure medication valproate sodium and related products, valproic acid and divalproex sodium, are contraindicated and should not be taken by pregnant women for the prevention of migraine headaches. This safety communication was based on the final results of the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study showing that children exposed to valproate products while their mothers were pregnant had decreased IQs at age 6 compared to children exposed to other anti-epileptic drugs. The difference in average IQ between these two groups varied between 8 and 11 points depending on the drug to which valproate was compared. Stronger warnings about use during pregnancy will be added

to the drug labels, and valproate's pregnancy category for migraine use will be changed from "D" (the potential benefit of the drug in pregnant women may be acceptable despite its potential risks) to "X" (the risk of use in pregnant women clearly outweighs any possible benefit of the drug). FDA recommended that valproate products should not be used in pregnant women for the prevention of migraine headaches. Valproate products should be used in pregnant women with epilepsy or bipolar disorder only if other treatments have failed to provide adequate symptom control.

In Hong Kong, there are 13 registered pharmaceutical products containing valproate and valproic acid and they are prescription only medicines. News regarding the increased risk of impaired cognitive development in children exposed during pregnancy with valproate or related products were released by FDA and Health Canada back in July 2011, and was reported in Drug News Issue No. 21. The matter was discussed in the meeting of the Registration Committee of the Pharmacy and Poisons Board in September 2011, and the Committee decided that the package insert of valproate or related products should be updated to include the appropriate safety information. In view of FDA's latest recommendation on the contraindicated use in pregnant women for the prevention of migraine headaches, a letter to healthcare professionals was issued on 7 May 2013 and the matter will be further discussed in the Registration Committee.

US: FDA approves label changes for zolpidem products, including new dosing and a recommendation to avoid driving the day after Ambien CR use

In January 2013, FDA announced the risk of next-morning impairment after use of insomnia drugs, and required lower recommended doses for extended-release forms of these drugs. On 14 May 2013, FDA announced that FDA had approved label changes specifying new dosing recommendations for all zolpidem products (Ambien, Ambien CR, and Edluar), which are widely prescribed sleep medications. FDA had approved these changes because of the known risk of next-morning impairment with these drugs. FDA also warned that patients who take the sleep medication zolpidem extended-release should not

drive or engage in other activities that require complete mental alertness the day after taking the drug because zolpidem levels can remain high enough the next day to impair these activities. This new recommendation has been added to the Warnings and Precautions section of the physician label and to the Patient Medication Guide for zolpidem extended-release (Ambien CR). The new dosing recommendations stated in FDA's January 2013 Drug Safety Communication were also updated.

In Hong Kong, there are 15 registered pharmaceutical products containing zolpidem which include immediate-release 5mg or 10mg tablets and modified-release 6.25mg or 12.5mg tablets. All of them are prescription only medicines indicated for the treatment of insomnia. Zolpidem is also controlled as psychotropic substance internationally including Hong Kong. A letter to healthcare professionals was issued on 11 January 2013 and the concern was reported in Drug News Issue No. 39. The matter was discussed in the meeting of the Registration Committee of the Pharmacy and Poisons Board in February 2013. The Registration Committee decided that DH should continue to remain vigilant on any updated news of zolpidem by other overseas regulatory authorities for further consideration when necessary.

EU / Canada / UK: Updates on the use of Diane 35 and generics

On 31 January 2013, the European Medicines Agency (EMA) announced that the French National Agency for the Safety of Medicine and Health Products (ANSM) planned to suspend the marketing authorisation for Diane 35 and its generics for acne treatment in France within 3 months, due to the risk of thromboembolism. On 17 May 2013, EMA alerted that despite the conclusion of the Pharmacovigilance Risk Assessment Committee (PRAC) that the benefits of Diane 35 and its generics outweigh the risks in a specific patient group, ANSM unexpectedly announced the decision to suspend the marketing authorisations of these medicines in France.

The French decision came at a time, when the process was not yet complete as the PRAC recommendation was the first step towards a common European Union (EU) approach. The PRAC recommendation would be considered by the

Co-ordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh). On 30 May 2013, the CMDh had endorsed by majority (26:1) the recommendation of the PRAC, which concluded that the benefits of Diane 35 and its generics outweigh the risks, provided that several measures are taken to minimise the risk of thromboembolism. These medicines should be used solely in the treatment of moderate to severe acne related to androgen sensitivity and/or hirsutism in women of reproductive age. Furthermore, Diane 35 and generics should only be used for the treatment of acne when alternative treatments, such as topical therapy and antibiotic treatment, have failed. Since Diane 35 and its generics act as hormonal contraceptives, women should not take these medicines in combination with other hormonal contraceptives. Concomitant use of Diane 35 and its generics with another hormonal contraceptive will expose women to a higher dose of oestrogen and increase the risk of thromboembolism. The risk of thromboembolism occurring with these medicines is low and well known. However, to minimise this risk, further measures should be implemented in addition to the updated product information. These include providing educational materials to prescribers and patients highlighting the risks of thromboembolism, for example a prescriber checklist to ensure that the risks, together with the signs and symptoms, are discussed with the patient.

In May 2013, both Health Canada and the Therapeutic Goods Administration (TGA) of Australia announced that the benefits of Diane 35 continue to outweigh the risks, when used as authorized. Similarly, the Medicines and Healthcare products Regulatory Agency (MHRA) of UK announced that there is no need for a woman who is feeling well to stop taking Diane 35 – also known as Dianette in the UK. If any woman has concerns about her treatment she should contact her doctor.

In Hong Kong, Diane-35 Tab (HK-43330) is registered by Bayer Healthcare Ltd. and there are nine generic products with same ingredients registered in Hong Kong. All are prescription only medicines indicated for the treatment of acne; other registered indications include androgenetic alopecia, mild forms of hirsutism and contraception. The package inserts have included

the precaution of blood clot. The issue was reported in Drug News Issue No. 39, and a letter to healthcare professionals was issued on 31 January 2013. In light of the announcements by EMA, Health Canada, MHRA and TGA, the matter will be discussed in the meeting of the Registration Committee of the Pharmacy and Poisons Board.

Australia: Dabigatran (Pradaxa) and risk of bleeding

On 23 May 2013, TGA informed health professionals that it completed two safety reviews and both reviews reinforced the importance of appropriate patient selection for the safe use of dabigatran. In particular, when making a decision to prescribe dabigatran, a careful assessment of the risk factors for bleeding needs to be undertaken. The updated safety information are:

1. a contraindication for concomitant use of dronedarone and dabigatran is added;
2. health professionals are reminded that dabigatran capsules should be stored and dispensed in the original packaging (blister pack or bottle). Repackaging dabigatran capsules increases the risk of exposure to moisture or humidity, potentially causing the medicine to breakdown and lose potency;
3. health professionals are advised that dabigatran may have an effect on the results of some pathology tests; and
4. up to 8 February 2013, a total of 1054 cases of adverse events were reported to TGA. Such cases include serious bleeding adverse events of the gastrointestinal and intracranial areas.

In Hong Kong, Pradaxa is an anticoagulant registered as 75mg capsules (HK-57316), 110mg capsules (HK-57315) and 150mg capsules (HK-60516) by Boehringer Ingelheim (HK) Ltd. and is a prescription only medicine. Safety alerts on Pradaxa had been released by various overseas regulatory authorities which had been reported in Drug News Issues No. 24, No. 25, No. 29, No. 31, No. 37 and No. 38. The safety issues were discussed in the meetings of the Registration Committee of the Pharmacy and Poisons Board in April 2012, December 2012 and April 2013. The decisions made by the Registration Committee in April 2012 and December 2012 were reported in

Drug News Issues No. 31 and No. 38 respectively. In April 2013, the Registration Committee discussed the issue of the use in patients with prosthetic heart valves, and decided that the sales pack label and/or package insert of the products should include additional contraindication of “prosthetic heart valves requiring anticoagulant treatment”. The package inserts of the products have been subsequently updated to include the latest safety information. DH will keep vigilant on any safety updates of the drug and actions taken by overseas regulatory authorities for consideration of any action deemed necessary.

US: Recommendation against prolonged use in pre-term labor for Magnesium Sulfate

On 30 May 2013, FDA advised healthcare professionals against using magnesium sulfate injection for more than 5-7 days to stop pre-term labor in pregnant women. This use of the drug is off-label, and is not approved by FDA. Administration of magnesium sulfate injection to pregnant women longer than 5-7 days may lead to low calcium levels and bone problems in the developing baby or fetus, including thin bones (osteopenia), and fractures. The shortest duration of treatment that can result in harm to the baby is not known. In light of this new safety information, the following information was being added to the drug label for Magnesium Sulfate Injection, USP 50%:

- a new Warning stating that continuous administration of magnesium sulfate injection beyond 5-7 days in pregnancy for the treatment of pre-term labor can cause low calcium levels and bone changes in the baby;
- a new Teratogenic Effects section conveying the potential harm to developing babies by changing the Pregnancy Category to D from A. Pregnancy Category D means there is positive evidence of human fetal risk, but the potential benefits from using the drug in pregnant women may be acceptable in certain situations despite its risks; and
- a new Labor and Delivery section emphasizing that continuous administration of magnesium sulfate injection to treat pre-term labor is not approved and that the safety and efficacy of use for this indication are not established. When used in pregnant women for conditions

other than its approved indication, magnesium sulfate injection should be administered only by trained obstetrical personnel in a hospital setting with appropriate obstetrical care facilities.

In Hong Kong, there are three registered injectable pharmaceutical products containing magnesium sulfate, which are indicated for the treatment and prevention of hypomagnesaemia, pre-eclampsia and eclampsia. In view of FDA's recommendations, a letter to healthcare professionals was issued on 31 May 2013. The matter will be discussed in the meeting of the Registration Committee of the Pharmacy and Poisons Board.

UK: MHRA response to published research paper concerning non-steroidal anti-inflammatory drugs (NSAIDs)

On 30 May 2013, MHRA had made the following statement in response to the research paper published in the Lancet concerning non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and Diclofenac and the risks of cardiovascular problems. Dr Sarah Branch, MHRA's Deputy Director for the Vigilance and Risk Management and of Medicines, said: “these findings in the Lancet are not new and confirm the conclusions reached in October 2012 by the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP). Non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and diclofenac are effective painkillers. A small increase in cardiovascular risk is associated with long-term use of ibuprofen and diclofenac at high doses. The short term use of ibuprofen at doses available without a prescription has not been associated with an increased risk. MHRA's current treatment advice for all NSAIDs is for people to use the lowest effective dose, for the shortest duration necessary to control symptoms. If people have any questions about their treatment they should contact their pharmacist or doctor.”

In Hong Kong, NSAIDs-containing products are registered pharmaceutical products with ingredients such as diclofenac, ibuprofen, naproxen, indomethacin, mefenamic acid and piroxicam. They are indicated for the treatment of arthritis and headache and many other painful conditions arising from fever and minor ailments. The cardiovascular risk of NSAIDs was reported in Drug News Issues

No. 24 and No. 36, and a letter to healthcare professionals was issued on 30 September 2011. The matter was discussed by the Registration Committee of the Pharmacy Poisons Board in February 2013, and the Committee concluded that NSAIDs-containing products other than external preparations should include the appropriate safety information, such as examples given as below:

A. Under “Dosage”: “Product name” should be used at the lowest effective dose for shortest possible time.

B. Under “Contraindications”: “Product name” is contraindicated:

- i. in patients with severe heart failure; and
- ii. for the treatment of peri-operative pain in the setting of coronary artery bypass graft surgery; history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy; active, or history of recurrent peptic ulcer/haemorrhage.

C. Under “Warnings and Precautions”:

i. Cardiovascular Risk:

NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

ii. Gastrointestinal Risk:

NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events.

iii. Renal Effects:

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in

renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

iv. Advanced Renal Disease:

No information is available from controlled clinical studies regarding the use of “Product name” in patients with advanced renal disease. Therefore, treatment with “Product name” is not recommended in these patients with advanced renal disease. If therapy must be initiated, close monitoring of the patient's renal function is advisable.

Canada: Revision to the Product Monographs (PMs) of non-nicotine smoking cessation aids Champix (varenicline tartrate) and Zyban (bupropion hydrochloride)

On 30 May 2013, Pfizer Canada Inc. and Valeant Canada LP, in collaboration with Health Canada, announced the revisions to the Product Monographs (PMs) for non-nicotine smoking cessation aids Champix (varenicline tartrate) and Zyban (bupropion hydrochloride). Champix is a smoking cessation pharmacological treatment to be used in conjunction with smoking-cessation counselling. Zyban is a smoking cessation pharmacological treatment to be used in conjunction with behavioural modification. In addition, Zyban is indicated for use with nicotine replacement therapy. The following key statements had been added to the PMs for the class of non-nicotine smoking cessation aids (Champix and Zyban):

Prior to a decision to prescribe a non-nicotine treatment, Champix or Zyban, thorough consideration should be given to the treatment option of nicotine replacement therapy. In many cases, nicotine replacement therapy should be tried before prescribing Champix or Zyban.

These revisions to the PMs were based on continuing post-marketing surveillance and mechanisms of action of non-nicotine products. The PM revisions and this communication were intended to reinforce the importance of a discussion with patients about the expected potential benefits and risks associated with the use of smoking cessation therapies.

Safety Update

In Hong Kong, Champix Tab 0.5mg (HK-55479), Champix Tab 0.5mg & 1mg (HK-55462) and Champix Tab 1mg (HK-55437) are registered by Pfizer Corp. HK Ltd. and Zyban Sustained-release Tab 150mg (HK-46946) is registered by GlaxoSmithKline Ltd. They are prescription only medicines indicated for smoking cessation. News on the potential risk of congenital cardiovascular malformations associated with the use of bupropion

had been released by HSA and reported in Drug News Issue No. 37. A letter to healthcare professionals was issued on 17 January 2013, and the matter will be discussed in the meeting of the Registration Committee of the Pharmacy and Poisons Board. DH will keep vigilant on any safety updates of the drug for consideration of any action deemed necessary.

Drug Recall

Batch recall of Weelgac-S Syrup (HK-12650)

On 3 May 2013, DH instructed a licensed drug wholesaler, National Pharmaceutical Co. Ltd., to recall from the shelves one batch of Weelgac-S Syrup (威力特效止咳水) (batch no. 421201) due to a quality issue. Weelgac-S Syrup, containing codeine, ephedrine and promethazine, is used for the relief of coughing. It can only be sold in pharmacy under the supervision of a registered pharmacist.

Under the DH's surveillance system, samples of the batch of Weelgac-S Syrup concerned were collected for testing by the Government Laboratory. Analytical results confirmed that the content of one of the active ingredients of the product, namely codeine, is less than that specified on the label (about 85 per cent of the labelled amount). The quality defect may affect the efficacy of the product.

According to the wholesaler, the product is manufactured by Guangzhou National Pharmaceutical Co Ltd in China. A total of 6,000 bottles of the affected batch were imported into Hong Kong in December 2012, and about 3,400 bottles were supplied to local pharmacies. DH had alerted the concerned parties about the matter and closely monitored the recall. As of 3 May 2013, DH had not received any adverse drug reaction reports in connection with the product. A press statement was released on the same day to alert the public of the recall.

Selling any drug not of the nature, substance or quality demanded by the purchaser is an offence under Section 52(1) of the Public Health and Municipal Services Ordinance (Cap 132). The maximum penalty is a \$10,000 fine and three months' imprisonment.

Recall of Benzo-Jel Topical Anesthetic Gel

On 3 May 2013, DH instructed a licensed drug wholesaler, Henry Schein HK Holdings Ltd., to recall from market all flavours of Benzo-Jel Topical Anesthetic Gel as they are unregistered pharmaceutical products in Hong Kong.

Benzo-Jel Topical Anesthetic Gel, labelled as containing 20 per cent benzocaine, is used as a local anaesthetic to be applied on the oral mucosa. Side-effects include dizziness, blurred vision, nausea and vomiting. They can only be sold in pharmacies under the supervision of registered pharmacists.

Upon the investigation of a public complaint, the premises of Henry Schein were raided and a quantity of different flavours of Benzo-Jel Topical Anesthetic Gel was seized. Hong Kong pharmaceutical product registration numbers were not found on the product labels. Preliminary investigation revealed that the products were imported into Hong Kong by Henry Schein and were supplied to local dentists.

DH had informed dentists and relevant professional bodies about the matter and closely monitored the recall. As of 3 May 2013, DH had not received any adverse drug reaction reports in connection with the product. A press statement was released on the same day to alert the public of the recall.

Under the Pharmacy and Poisons Ordinance (Cap 138), sale or possession of unregistered pharmaceutical products are offences liable to the maximum penalty of a fine of \$100,000 and two years' imprisonment for each offence.

Drug Recall

Recall of Apo-Simvastatin Tablets 10mg, 20mg, and 40mg packed in 30's boxes (HK-51718, HK-51719, and HK-51793)

On 7 May 2013, DH instructed a licensed drug wholesaler, Hind Wing Co. Ltd. (Hing Wing), to recall from shelves three Apo-Simvastatin products packed in 30's boxes, namely Apo-Simvastatin Tablets 10 mg, 20mg, 40mg because unapproved product insert was used in the products packages. Apo-Simvastatin tablets, containing simvastatin, are prescription only medicines indicated for hypercholesterolaemia. Side effects include gastrointestinal disturbances, dizziness, neuropathy and myalgia. They can only be sold in pharmacy according to doctor's prescription and under the supervision of registered pharmacist.

Under the surveillance system of DH, it was found that the above products were using an unapproved product insert, which rendered the products unregistered pharmaceutical products. According the registration record, the products do not have any product insert.

According to Hind Wing, the products were supplied to private doctors, local pharmacies and private hospitals. DH had closely monitored the recall. As of 7 May 2013, DH had not received any adverse drug reaction reports in connection with the product. A press statement was released on the same day to alert the public of the recall.

Drug Incident

Public urged not to buy or use slimming products with undeclared and banned drug ingredients

In May 2013, DH appealed to members of the public not to buy or consume two slimming products called “STB Summit of the Thin Body S Woman Degreasing Burning Pill” (速效溶脂燃燒丸) and “Lightning 10.0+ Reduces Weight” as they may contain multiple undeclared and banned drug ingredients that might be dangerous to health.

DH was notified by the Hospital Authority (HA) about two patients feeling unwell after consumption of the products. Investigation showed that both products were purchased from the Internet. The details of these two cases were summarized as follows:

Patients	Products consumed	Symptoms developed	Drug ingredients detected in laboratory tests
A 24-year-old female	“STB Summit of the Thin Body S Woman Degreasing Burning Pill” (速效溶脂燃燒丸)	Psychiatric symptoms including suicidal thoughts, persecutory delusion and auditory hallucination	Sibutramine, phenolphthalein and sildenafil
A 21-year-old female	“Lightning 10.0+ Reduces Weight” pills	Psychiatric symptoms including suicidal thoughts and visual hallucination	Sibutramine, phenolphthalein and indomethacin

Sibutramine is a Part I poison and was once used as an appetite suppressant. Since November 2010, all products containing sibutramine have been banned in Hong Kong because of an increased cardiovascular risk. Phenolphthalein was once used for treating constipation but has been banned in Hong Kong for its possible cancer-causing effect.

Drug Incident

Products containing sildenafil are prescription drugs for the treatment of erectile dysfunction and should only be supplied at pharmacies under the supervision of a registered pharmacist and upon the production of a doctor's prescription. The side effects of sildenafil include low blood pressure, headache, vomiting, dizziness and transient vision disturbances. It may interact with some drugs (such as nitroglycerin for treatment of angina) and cause a decrease in blood pressure to dangerous levels. Improper use of sildenafil may pose serious health risks, especially for patients with heart problems.

Indomethacin is a non-steroidal anti-inflammatory drug used to relieve pain and inflammation. Its known side effects include gastrointestinal discomfort, nausea, peptic ulcer and renal impairment. It is well known that users will have increased risks of developing complications like gastrointestinal ulcers, some of which may be undetected until more serious complications like gastrointestinal bleeding set in.

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

The press statement related to the cases was issued on 16 May 2013.

Persons arrested for sale of unregistered pharmaceutical products with controlled drug ingredients on the Internet

In May 2013, four joint operations were conducted by DH and the Police resulting in the arrests of various persons. Members of public are urged not to buy or consume unregistered pharmaceutical products as they have not been evaluated by the Pharmacy and Poisons Board and their safety, quality and efficacy are not guaranteed. Press statements related to the cases were issued on the days of the operations. The details of these cases are summarized as follows:

Case No.	Products concerned	Drug ingredients	Indications	Arrested persons
1.	“Men's Rogaine Extra Strength 5% Minoxidil Topical Solution”	Minoxidil (a Part I poison)	Commonly used for the treatment of hair loss.	A 67-year-old man
2.	“AcaiBerry Living-XS” capsules	Sibutramine and phenolphthalein	Please refer to the above news for details.	A 40-year-old woman
3.	“4C Cosmoslim” capsules (4C 鑽石瘦身)			A 23-year-old woman
4.	“FLUCORT f” cream	Fluocinolone (a Part I poison) and neomycin (an antibiotic)	- Fluocinolone is commonly used for the treatment of inflammatory diseases. - Neomycin is used topically for the treatment of infections of skin, ear, and eye.	A 38-year-old woman

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 I poisons should be sold at registered pharmacies under the supervision of registered pharmacists. Illegal sale or possession of Part I 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.

Drug Incident

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.

Retail shops raided for selling and possession of unregistered pharmaceutical products

In May 2013, two joint operations were conducted by DH and the Police resulting in the shops raided for selling and possession of unregistered pharmaceutical products. Press statements related to the cases were issued on the days of the operations. The details of these cases were summarized as follows:

Case No.	Products concerned	Drug ingredients	Indications	Locations
1.	A number of unregistered pharmaceutical products, e.g. Country Life Mega CoQ 10, Country Life Natural Vitamin A & D3, Country Life Arthro-Joint & Muscle Support Factors, etc.	Vitamins and /or glucosamine	- Vitamin supplementation for people who are at risk of deficiency. - Glucosamine is indicated for joint problems.	Admiralty
2.	Some unregistered pharmaceutical products with product names in Japanese	Vitamins and /or glucosamine		Mong Kok

News in Brief

Deregistration of pharmaceutical products containing combination of corticosteroid and non-steroidal anti-inflammatory drug

On 2 May 2013, DH announced the decision by the Pharmacy and Poisons (Registration of Pharmaceutical Products and Substances: Certification of Clinical Trial/Medicinal Test) Committee of the Pharmacy and Poisons Board to deregister pharmaceutical products containing the combination of corticosteroid and non-steroidal anti-inflammatory drug (NSAID) with effect from 1 January 2014, because the benefits of the products no longer outweigh their risks.

The Committee's decision was made at its meeting on 30 April 2013, after taking into consideration that the risk of gastro-intestinal bleeding and ulceration associated with NSAID would be increased when it is used in combination with corticosteroid and that DH had received local reports of adverse drug reactions related to such combination of drug ingredients. The Committee noted that patients should not stop using the products abruptly as sudden withdrawal of corticosteroid may lead to serious health consequences. Therefore, it decided that the deregistration would take effect on 1 January 2014, to provide a transition period for doctors to switch to alternative treatments for their patients. DH would issue letters to healthcare professionals to inform them of the Committee's decision and related matters.

Both corticosteroids and NSAIDs have anti-inflammatory effects and have been used for the symptomatic relief of rheumatoid pain. Both of them may lead to gastro-intestinal bleeding and the risk is increased when corticosteroid and NSAID are used concomitantly.

News in Brief

Currently, there are 66 registered pharmaceutical products containing the combination of corticosteroid and NSAID as ingredients manufactured by six local manufacturers and they are all prescription only medicines, which can only be sold by pharmacies under the supervision of registered pharmacists upon doctors' prescriptions.

When the Committee's decision takes effect on 1 January 2014, all drug manufacturers, wholesalers and retailers must stop selling or distributing pharmaceutical products containing the combination of corticosteroid and NSAID. The manufacturers are also required to recall the products concerned from shelves by 31 December 2013. DH will take surveillance action and prosecute any trader for illegal possession or sale of such products afterwards.

Healthcare professionals should contact patients taking medicines containing the combination of corticosteroid and NSAID to review their treatment plans as soon as possible. Patients should be advised not to stop using these medicines abruptly as sudden withdrawal of corticosteroid may lead to serious health consequences.

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: 2186 9845

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.