Drug News
藥 物 情 報

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This is a digest of local and overseas drug safety news and information released by the Drug Office of the Department of Health in the period as stated above. 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

EU: Benefit –risk balance of pholcodine-containing cough medicines remained positive

On 18 November 2011, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) had completed the review of the potential risk of cross- sensitisation between the use of pholcodine-containing cough medicines and neuromuscular blocking agents (NMBAs) used in anaesthesia during surgery, which might lead to anaphylactic reactions. The Committee reviewed all available safety and efficacy data on pholcodine-containing cough medicines and found no firm evidence to substantiate the above risk.

As reported in Issue No. 17 of Drug News, the review was initiated in February 2011 because of concerns arose after a study showing a decrease of reports of anaphylactic reactions to NMBAs in Sweden and Norway following the withdrawal of pholcodine from the market of the two countries.

In view of the existing data confirming a positive benefit-risk balance, CHMP decided that pholcodine -containing medicines should remain available for the treatment of non-productive (dry) cough in children and adults. The marketing authorisation of pholcodine should be maintained in all European Union (EU) Member States where it had been authorised and no further regulatory action was necessary. On the other hand, CHMP considered that the manufacturers should conduct a post-marketing study to investigate the possible association between pholcodine and anaphylactic reactions to NMBAs.

In Hong Kong, there are about 37 registered products containing pholcodine which is a centrally acting cough suppressant. They must be sold under the supervision of pharmacist. The Department of Health (DH) will keep vigilant against any updated safety news of the drugs.

US, Canada: Removal of breast cancer indication from the product label of Avastin (bevacizumab)

Following the recommendation of removing the breast cancer indication from the label for Avastin by the Centre for Drug Evaluation and Research (CEDR) of the US Food and Drug Administration (FDA) in December 2010, a two-day hearing initiated by its manufacturer, Genentech, was held on 28-29 June 2011. On 18 November 2011, the FDA announced the decision to remain revoking the approval of its breast cancer indication.

Avastin was approved for metastatic breast cancer under the FDA's accelerated approval program in February 2008, which new drugs were approved to be marketed while confirmatory clinical trials were conducted. A comprehensive review including 2 clinical trials showed that the drug did not provide sufficient benefit (in terms of delay in tumor growth, prolonged survival and improvement in quality of life) to outweigh its potentially life-threatening side effects (including severe high blood pressure; bleeding and hemorrhaging; heart attack or heart failure; and the development of perforations in different parts of the body such as the nose, stomach, and intestines) to patients with metastatic breast cancer. As a result, FDA's CEDR proposed to withdraw approval of this indication of Avastin.

Avastin would still remain on the US market as an approved treatment for certain types of colon, lung, kidney and brain cancer (glioblastoma multiforme).

After a thorough review of scientific data and taking

the advice provided by an independent Expert Advisory Panel into consideration, Health Canada annouced on 28 November 2011 the decision to direct Hoffmann-La Roche Ltd., the manufacturer of Avastin, to remove the use for metastatic breast cancer from Avastin's label. The decision did not affect other approved indications of Avastin.

In Hong Kong, there are 6 pharmaceutical products containing bevacizumab registered under the name of Avastin Roche by Roche HK Ltd. They are all prescription medicines indicated for treatment of metastatic breast, colorectal, lung, renal cancer and glioblastoma. Safety news on the matter released by FDA and EMA in December 2010 was reported in Issue No. 15 of Drug News. In response, DH issued a letter to healthcare professionals on 17 December 2010. The matter was discussed in the meeting of Registration Committee of the Pharmacy and Poisons Board on 11 May 2011. The Committee decided to adopt EMA's recommendation that Avastin should only be used in combination with paclitaxel, a taxane for the treatment of metastatic breast cancer, whilst it should no longer be used in combination with another taxane, docetaxel for such treatment. In view of FDA's decision on the removal of breast cancer indication, another letter has been issued on 19 November 2011 to healthcare professionals. The matter was further discussed in the meeting of the Registration Committee of the Pharmacy and Poisons Board on 22 February 2011 and the Committee decided that Avastin in combination with paclitaxel should be retained as a treatment option for metastatic breast cancer in Hong Kong. DH will keep vigilant against any updated safety news of the drug.

EU, UK, China, Singapore: Regulatory actions following the detection of the shortcomings in quality assurance at Ben Venue Laboratories

Following the identification of the shortcomings in quality assurance during a good manufacturing practice (GMP) inspection at Ben Venue Laboratries (BVL) in Ohio, US by EMA in March 2011, a joint GMP inspection of the site by the medicines regulatory agencies of the United Kingdom (UK), the Medicines and Healthcare products Regulatory Agency (MHRA), AFFSAPS of France, and US, FDA, was conducted on 7-11 November 2011. Several shortcomings in the quality management system were highlighed, particularly in relation to the aseptic filling process in the North Complex of the BVL facility. During the inspection, BVL decided to cease all manufacture and distribution of medicines from its site and to increase GMP surveillance and investigate the GMP issues identified. In response, regulatory actions were conducted in various countries including EU, UK, Singapore and China, as shown in Table 1 below.

Table 1. Regulatory actions taken by different countries

<table>
<tr><th>Products manufactured by BVL</th><th>EU (CHMP)</th><th>UK (MHRA)</th><th>Singapore (HSA)</th><th>China (State Food and Drug Administration) (SFDA)</th></tr>
<tr><td>Caelyx</td><td colspan="3">*Supply should only be available in patients already on Caelyx but not for new patients.</td><td>Recalled and switched to alternative supplies</td></tr>
<tr><td>Ceplene</td><td rowspan="2">*Supply should be available to patients.</td><td colspan="3" rowspan="2">Not marketed</td></tr>
<tr><td>Torisel</td></tr>
<tr><td>Busilvex/ Busulfex</td><td colspan="2" rowspan="2">Recalled</td><td>Switched to a new supply source</td><td>Not marketed</td></tr>
<tr><td>Velcade</td><td>Switched to alternative supplies</td><td>*Supply should be available to patients already on Velcade provided they understood the risks and consented to use it.</td></tr>
</table>

Products manufactured by BVL	EU (CHMP)	UK (MHRA)	Singapore (HSA)	China (State Food and Drug Administration) (SFDA)
Vidaza	Recalled	Affected batches not available	Not marketed	
Ecalta	Recalled	Not marketed		
Luminity				
Vistide				
Angiox	Not marketed			
Cayston				
Mepact				
Soliris				
Vibativ				

* BVL was the only manufacturer and the product was essential for treatment.

In Hong Kong, there are 13 registered pharmaceutical products manufactured by BVL in US as listed in Table 2 below. Eight of them have been imported into Hong Kong. Among those eight products, there is no remaining stock for Neurolite for Inj. with Buffer Vial and Cardiolite for Inj. The former one had previously been recalled in September 2011 while the latter one did not have stock in Hong Kong since August 2011. Four products are currently available, namely Bicnu for Inj. 100mg, Busulfex Inj. 6mg/ml, Caelyx Conc for Infusion 2mg/ml and Velcade for Inj. 3.5mg. As there were no alternatives to replace the use of these drugs in the market and these drugs were considered to be essential to meet patients' needs, no recall action was initiated for these items. However, healthcare providers were advised to weigh the benefits against the potential risk of batch contamination when they considered continuing the treatment for existing patients. Nevertheless, no new patients should be started on treatment. They should monitor patients intensively on the use of these four drugs and report any adverse drug reactions and relevant safety concerns, such as sepsis. Recall of the remaining two imported products, Vidaza for Inj. 100mg and Eraxis for Inj. 100mg, were conducted, on 23 November and 12 December 2011 respectively as there were replacements in the market.

On both days of recall, DH issued press statements and letters to inform general public and healthcare professionals respectively on the matter. DH will keep vigilant against any updated news of BVL. The details of the two recalls were mentioned in the section of "Drug Recall" of this Drug News.

Table 2. Locally registered pharmaceutical products manufactured by BVL in US

Item	Product Name	HK Reg No. (Legal Classification)	Active Ingredient	Medicinal Class	Situation in HK
1.	Vidaza for Inj 100mg	HK-55407 (Prescription drug)	Azacitidine	Anti-neoplastic drug	Recall from market was instructed on 23 Nov 2011
2.	Eraxis for Inj 100mg	HK-57097 (Prescription drug)	Anidulafungin	Anti-fungal drug	Recall from market was instructed on 12 Dec 2011
3.	Bicnu for Inj 100mg	HK-05144 (Prescription drug)	Carmustine	Anti-neoplastic drug	Remain on market as there is no alternatives

Item	Product Name	HK Reg No. (Legal Classification)	Active Ingredient	Medicinal Class	Situation in HK
4.	Busulfex Inj 6mg/ml	HK-50627 (Prescription drug)	Busulphan	Anti-neoplastic drug	Remain on market as there is no alternatives
5.	Caelyx Conc for Infusion 2mg/ml	HK-43397 (Prescription drug)	Doxorubicin	Anti-neoplastic drug	Remain on market as there is no alternatives
6.	Velcade for Inj 3.5mg	HK-53329 (Prescription drug)	Bortezomib	Anti-neoplastic drug	Remain on market as there is no alternatives
7.	Cardiolite for Inj	HK-43085 (Over the counter)	Tetrakis copper tetrafluoroborate	Cardiac imaging agent	Currently no stock
8.	Neurolite for Inj with Buffer Vial	HK-43086 (Over the counter)	Bicisate dihydrochloride	Radioactive agent for diagnostic use	Recalled in Sept 2011
9.	Amevive for IM Inj 15mg	HK-54924 (Prescription drug)	Alefacept	Immunosuppressive drug	Not marketed in HK
10.	Amphocil for Infusion 50mg	HK-42397 (Prescription drug)	Amphotericin B	Anti-fungal drug	Not marketed in HK
11.	Amphocil for Infusion 100mg	HK-42398 (Prescription drug)	Amphotericin B	Anti-fungal drug	Not marketed in HK
12.	Pulmolite for Inj	HK-43127 (Prescription drug)	Stannous Chloride, Albumin Human	Radioactive agent for diagnostic use	Not marketed in HK
13.	Velcade for Inj 1mg	HK-58055 (Prescription drug)	Bortezomib	Anti-neoplastic drug	Not marketed in HK

Canada: Complex sleep behaviours associated with Sublinox (zolpidem tartrate)

On 30 November 2011, Meda Valeant Pharma Canada Inc., in consultation with Health Canada, informed healthcare professionals concerning the association of Sublinox with complex sleep behaviours. Sublinox is a sublingual formulation of zolpidem that was recently authorised for use in adults and indicated for the short-term treatment and symptomatic relief of insomnia in Canada. Zolpidem had been reported in association with cases of complex sleep behaviours, where people rose from bed while not fully awoke and engaged in unknowingly, but potentially dangerous activities which they did not remember doing the following morning, such as driving a car or leaving the house. Prescribers were reminded of the followings when using the medication:

- Sublinox is contraindicated in patients with a personal or family history of somnambulism.
- Sublinox is not to be taken with alcohol.
- Complex sleep behaviours have been reported in patients using CNS-active drugs in combination with zolpidem.
- Treatment with Sublinox should be immediately discontinued in patients who

report complex sleep behaviours.

It was advised to counsel patients, their families, and caregivers on the benefits, risks and appropriate use of Sublinox. The failure of insomnia to remit after 7 to 10 days of treatment might warrant for further evaluation of a primary psychiatric and/or medical illness. Patient selection was important before prescribing this medication.

In Hong Kong, there are 14 registered pharmaceutical products containing zolpidem and none of them is in the sublingual formulation. They are all prescription medicines and used for short term management of insomnia. In view of Health Canada's recommendation, DH issued letters to healthcare professionals on 6 December 2011. The matter will be discussed in the meeting of the Registration Committee of the Pharmacy and Poisons Board.

Canada: Serious liver adverse effects associated with high dose of Ursodiol (ursodeoxycholic acid)

On 1 December 2011, the manufacturers of ursodiol (Aptalis Pharma Canada Inc., Dominion Pharmacal, Pharmascience Inc., Pharmel Inc., Teva Canada Ltd.), in consultation with Health Canada, informed healthcare professionals about an increased risk of serious liver adverse effects after taking twice the recommended dose of ursodiol (ursodeoxycholic acid, UDCA). In a 5-year randomized, double-blind, clinical trial, 150 primary sclerosing cholangitis (PSC) patients were treated with placebo or twice the recommended dose of ursodiol. Patients taking high dose ursodiol were found to have improvements in liver function tests but higher risk for death, liver transplantation or minimal listing criteria and serious adverse events (including varices, cirrhosis, and cholangiocarcinoma) compared to the placebo group. The Product Monographs in Canada for ursodiol had been revised to describe the clinical trial, and remarked that improved serum liver tests (e.g. AST, ALP) did not always correlate with an improved liver disease status. Monitoring of GGT, alkaline phosphatase, AST, ALT and bilirubin every month for three months after start of therapy, and every six months thereafter were recommended. It was advised to discontinue treatment if the levels of these parameters increased.

In Hong Kong, there are 10 over-the-counter pharmaceutical products containing UDCA registered and 8 of them contain UDCA as single ingredient. The approved indication of UDCA is for treatment of cholesterol gallstones and primary biliary cirrhosis. DH has contacted the Health Canada for the details of the clinical trials concerned and will closely monitor any further updates made by Health Canada and other regulatory authorities. In view of Health Canada's recommendation, DH issued a letter to healthcare professionals and press statement on 6 December 2011. The matter will be discussed in the meeting of the Registration Committee of the Pharmacy and Poisons Board.

Canada: Reports of severe ocular complications leading to blindness following unauthorized intravitreal injection of Avastin (bevacizumab)

On 2 December 2011, Hoffmann-La Roche Limited (Roche), in consultation with Health Canada, informed healthcare professionals that clusters of serious ocular complications, including acute ocular inflammation, endophthalmitis, and infectious endophthalmitis resulting in blindness, associated with intravitreal injection of Avastin were reported in US (Florida, Tennessee, and California). While the incidences were still under investigation, it was possible that the events of blindness from streptococcal endophthalmitis in Florida were due to repackaging of Avastin without proper aseptic technique. Avastin was not formulated for intravitreal use. Its production methods, formulation and dosages were specifically developed for intravenous use in the oncology setting.

In Hong Kong, Avastin Roche is registered by Roche Hong Kong Limited. It is a prescription medicine for treatment of cancer. In view of Health Canada's report, DH issued a letter to healthcare professionals on the importance of the safe use of Avastin Roche on 8 December 2011. DH will keep vigilant against any updated safety news of the drug.

US, Canada: Multaq (dronedarone) - increased risk of death or serious cardiovascular events

On 19 December 2011, US FDA announced the completion of a safety review on Multaq (dronedarone) which was initiated in July 2011 as reported in Issue No. 22 of Drug News. The review

showed that Multaq increased the risk of serious cardiovascular events, including death, when used by patients in permanent atrial fibrillation (AF). The review was based on data from two clinical trials, PALLAS and ATHENA. PALLAS, a study to evaluate the effectiveness of Multaq in elderly patients with permanent AF, was prematurely stopped in July 2011 because of the increased risk of death, stroke and hospitalization for heart failure. ATHENA was a study showing the use of Multaq could significantly reduced the risk of hospitalization due to cardiovascular events or death in patients with paroxysmal or persistent AF or atrial flutter which led to the approval of Multaq. The drug label of Multaq was now revised with the following changes and recommendations:

- Healthcare professionals should not prescribe Multaq to patients with permanent AF because Multaq doubles the rate of cardiovascular death, stroke and heart failure in such patients.
- Healthcare professionals should monitor heart rhythm by electrocardiogram at least once every 3 months. If the patient is in AF, Multaq should be stopped or, if clinically indicated, the patient should be cardioverted.
- Multaq is indicated to reduce hospitalization for AF in patients in sinus rhythm with a history of paroxysmal or persistent AF.
- Patients prescribed Multaq should receive appropriate antithrombotic therapy.

In Canada, Sanofi-aventis Canada Inc. had also updated the Product Monograph of Multaq similar to the recommendations of the FDA, announced by Health Canada on 5 December 2011.

In Hong Kong, Multaq is registered by Sanofi-Aventis HK Ltd. and is a prescription medicine indicated to reduce the risk of cardiovascular hospitalization in patients with atrial firbrillation or atrial flutter. Previous safety alerts on the risk of injuries to the liver, lung as well as cardiovascular system had been released by the EMA and other medicines regulatory authorities and reported in the previous issues of Drug News (Issue No. 15, 16, 22 and 24). Letters to healthcare professionals were issued on 12 and 22 July and 23 September 2011. The matter had been discussed in the meeting of the Registration Committee of the Pharmacy and Poisons Board on 28 February 2012 and the Committee decided that the sales pack or package insert of dronedarone-containing products should be updated to include safety information regarding the associated risk of injury to the liver, lung and heart that is in line with EMA's latest approved product information.

Australia: New contraindications, precautions and dosage recommendations of Simvastatin

On 6 December 2011, TGA of Australia advised healthcare professionals to limit the prescribing of high dose (80 mg/day) simvastatin and to be aware of new contraindications and precautions for the use of simvastatin with other medicines. TGA recommended that 80mg/day simvastatin should only be used in patients at high risk of cardiovascular complications who had not achieved their treatment goals on lower doses. Patients on high dose simvastatin and those taking certain other medicines had an increased risk of developing myopathy (muscle weakness) and, more rarely, rhabdomyolysis. Concomitant administration of simvastatin with the medicines including gemfibrozil, cyclosporine, danazol and potent CYP3A4 inhibitors such as itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, nefazodone and HIV protease inhibitors was contraindicated. New specific precautions (such as lower recommended simvastatin doses) were set for patients taking medicines including moderate inhibitors of CYP3A4, amiodarone, the calcium channel blockers such as verapamil, diltiazem and amlodipine, fibrates other than gemfibrozil, niacin ($\geqq$1g/day) and colchicine. The Product Information of simvastatin-containing products in Australia would be updated.

In Hong Kong, there are around 120 simvastatin-containing products registered and all are prescription medicines for treatment of hypercholesterolaemia. New safety recommendations of simvastatin regarding dosage, contraindications and dose limitations released by US FDA in June 2011 have been reported in Issue No. 20 of Drug News and a letter to healthcare professionals was issued on 9 June 2011. The matter was discussed in the meeting of the Registration Committee of the Pharmacy and Poisons Board on 6 September 2011. The Committee decided that the sales pack label and/or package insert of the

products containing simvastatin should include the appropriate warnings. In view of TGA's recommendation, DH has issued another letter to healthcare professionals on 7 December 2011 and the matter will be further discussed in the meeting of the Registration Committee of the Pharmacy and Poisons Board.

US: Updates on the safety review of risk of adverse cardiovascular events with Attention -Deficit/Hyperactivity Disorder (ADHD) medicines

Further to the annoucement made by FDA on 1 November 2011 as reported in Issue No. 25 of Drug News that treatment with medications for ADHD in children and young adults did not associate with adverse cardiovascular events, FDA released results of 2 relevant studies in adults which were recently completed on 12 December 2011. The 2 studies evaluated heart attacks, sudden deaths and stroke among adults treated with ADHD medications which did not show an increased risk of serious adverse cardiovascular events. Patients were advised to continue to use their medicine for the treatment of ADHD as prescribed by their healthcare professionals. Healthcare professionals were advised not to use stimulant products and atomoxetine in patients with serious heart problems, or for whom an increase in blood pressure or heart rate would be problematic. They were advised to periodically monitored patients treated with ADHD medications for changes in heart rate or blood pressure.

In Hong Kong, products containing methylphenidate and atomoxetine are registered and are prescription medicines. DH will keep vigilant against any new safety news of the drugs.

US: Safety update on the potential risk of newborn babies with the use of selective serotonin reuptake inhibitor antidepressants during pregnancy

On 14 December 2011, US FDA annouced that there was still insufficient scientific evidence to conclude that the use of selective serotonin reuptake inhibitor (SSRI) antidepressants by women during pregnancy would cause Persistent Pulmonary Hypertension of the Newborn (PPHN), a rare heart and lung condition. After completing the review on studies about the potential risk, it was found that the results were conflicting and it would be premature to reach any conclusion about a possible link between SSRI use in pregnancy and PPHN.

Therefore, FDA advised healthcare professionals not to alter their current clinical practice of treating depression during pregnancy. In addition, it would update the SSRI drug labels when new data regarding the use of SSRI and PPHN became available.

In Hong Kong, there are around 100 SSRI antidepressants registered and all are prescription medicines. In light of FDA's recommendation, a letter to healthcare professionals was issued on 15 December 2011 and the matter will be discussed in the meeting of the Registration Committee of the Pharmacy and Poisons Board.

EU: Benefit-risk balance of somatropin-containing medicines remained positive

On 21 December 2011, CHMP of the EMA announced the completion on the safety review of somatropin-containing medicines which was initiated in December 2010 as reported in Issue No. 14 of Drug News. The review stemed from a long-term epidemiological study which suggested a potential increased risk of mortality with somatropin therapy in children with idiopathic lack of growth hormone and idiopathic or gestational short stature compared with the general population. After considering all available data on the safety of somatropin-containing medicines, CHMP concluded that the benefit-risk balance of the medicines remains positive in the approved indications and doses. The CHMP remarked that the epidemiological study had significant methodological limitations and that the other safety data examined did not corroborate a potentially higher risk of mortality associated with somatropin-containing medicines. The existing contraindications, warnings and precautions for these medicines in the EU were harmonised to emphasise that somatropin must not be used if there is any evidence of a tumour activity and that the recommended maximum daily dose should not be exceeded. The CHMP pledged to review any new important relevant data if emerged and communicate the outcome as appropriate.

In Hong Kong, there are 13 registered pharmaceutical products containing somatropin and all of them are prescription medicines. Somatropin

is a synthetic human growth hormone indicated for long-term treatment of children with pituary growth failure due to inadequate production and secretion of growth hormone, and growth failure due to Turner's syndrome. Similar review has been conducted by FDA since December 2010 as reported in Issue No. 15 of Drug News. Interim result released by FDA in August 2011 also suggested inconclusive evidence regarding the link between somatropin and an increased risk of death. DH will keep vigilant against any updated safety news of the drug.

Canada, EU, UK: Review of aliskiren-containing medicines following termination of ALTITUDE study

On 20 December 2011, Novartis, the manufacturer of aliskiren, announced to terminate a multinational clinical trial known as the ALTITUDE study (**A**Liskiren **T**rial **I**n **T**ype 2 diabetes **U**sing cardio-renal **D**isease Endpoints), which involved 8,606 patients from 36 countries. The ALTITUDE study was a randomized, double-blind, placebo-controlled phase III study started in October 2007 to evaluate the potential benefits of aliskiren in reducing the risk of cardiovascular and renal events in high-risk patients with type 2 diabetes and renal impairment. They were given aliskiren 300mg in addition to either an angiotensin converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB).

The decision was made based on the recommendation of the independent Data Monitoring Committee (DMC) overseeing the study. The interim data showed no benefit with aliskiren and an increased incidence of non-fatal stroke, renal complications, hyperkalemia and hypotension among patients receiving aliskiren and a standard anti-hypertensive compared with patients who received a placebo. As a precautionary measure, Novartis ceased the promotion of aliskiren with an ACE inhibitor or ARB. Patients taking the drug were advised not to stop the treatment until they had seen their doctors in view of the importance of controlling high blood pressure.

In response to the announcement of Novatis, safety review of aliskiren was initiated by medicines regulatory authorities in different countries.

Situation in Canada

Aliskiren is currently authorized in Canada for use either alone or in combination with other drugs including ACE inhibitors and ARBs to control high blood pressure. Health Canada was evaluating available safety data, including information from Novartis along with other regulators internationally, to determine the impact on the risk-benefit profile of aliskiren for appropriate regulatory action as necessary such as strengthening and updating the drug labelling information with new safety information.

Situation in the EU and UK

In the EU, aliskiren is approved for the treatment of essential hypertension. The CHMP of the EMA started a review to assess the impact of data from the ALTITUDE study on the balance of benefits and risks of aliskiren-containing medicines in their approved indication. As a precautionary measure, in addition to those advices given to patients by Novartis, CHMP advised doctors not to prescribe aliskiren-containing medicines to diabetic patients in combination with ACE inhibitors or ARBs. They were advised to review the treatment of patients taking aliskiren at a routine (non-urgent) appointment, stop aliskiren and consider alternative treatments for diabetic patients concomitantly taking ACE inhibitors or ARBs.

In Hong Kong, there are 10 registered pharmaceutical products containing aliskiren and all are prescription medicines. Aliskiren, a direct renin inhibitor, is indicated for treatment of essential hypertension. DH was informed by the company on the early termination of the ALTITUDE study on 20 December 2011. A letter to healthcare professionals was then issued on 21 December 2011. The matter will be discussed in the Registration Committee of the Pharmacy and Poisons Board.

Australia: Advice about revaccination of Pneumovax 23

In March 2011, TGA of Australia started a review of a cluster of severe local injection site reaction associated with Pneumovax 23 vaccine. As reported in Issue No. 18 and 19 of Drug News, a batch of Pneumovax 23 was subsequently recalled in late March and an interim advice not to administer a second or subsequent dose of Pneumovax 23 was disseminated to health professionals in April as precautionary measures.

On 23 December 2011, TGA announced the review result. The adverse events were found to be

unrelated to the batch recalled. It was concluded that the increased numbers of reports of severe reactions were a result of the known high rates of local reactions; the increased number of people having a repeat dose following the inclusion of Pneumovax 23 in the National Immunisation Program in 2005 with revaccination after five years; and the increased reporting that followed the publicity of the batch recall. TGA is advising that revaccination with Pneumovax 23 can be undertaken in accordance with the approved product information.

In response, the Product Information (PI) of Pneumovax 23 was revised to include the following recommendations on revaccination:

- Revaccination should not be given routinely to immunocompetent individuals.
- Revaccination should be considered for patients at a high risk of serious pneumococcal disease, provided that at least five years has passed since the previous dose of Pneumovax 23.

The recommendations of Pneumovax 23 in the National Immunisation Program (NIP) were revised accordingly. TGA recommended to revaccinate Pneumovax according to the approved PI. Besides, patients who had been vaccinated with Pneumovax 23 were advised to consult their doctor for the need of revaccination.

In Hong Kong, Pneumovax 23 is registered by Merck Sharp & Dohme (Asia) Ltd. and is a prescription medicine used for immunisation against infections of pneumococcal bacteria. The local approved product recommendation for revaccination is in-line with the TGA's current recommendation, that revaccination of immunocompetent persons previously vaccinated with the vaccine is not routinely recommended. However, a second dose of vaccination is recommended for persons older than 2 years of age who are at highest risk of serious pneumococcal infection and those likely to have a rapid decline in pneumococcal antibody levels, provided that the second dose was administered at least five years after the first dose. Information about injection site reactions is included in the local approved package insert. In view of the updated TGA's recommendation, a letter to healthcare professionals was issued on 28 December 2011.

China: Risk of severe allergic reactions associated with vitamin K1 injection

On 26 December 2011, China SFDA alerted the public about the risk of severe allergic reactions associated with vitamin Kl injection. According to the National Center for Adverse Drug Reaction (ADR) Monitoring database, there were 893 reports of serious ADR associated with the injection of vitamin Kl during the period from 1 January 2004 to 31 May 2011. Among them, 328 cases (36.7%) were anaphylactic shock. Severe allergic reactions were found to be the most outstanding ADR. Further analysis revealed that the inappropriate clinical use of vitamin K1 injection, such as unapproved indication, overdose and wrong route of administration, increased the risk of adverse events.

SFDA advised healthcare professionals to check if the patients were allergic to vitamin Kl injection before initiating treatment, closely monitor the patients when giving the injection and stop the drug once any symptoms of allergy occurred. They were advised to prescribe vitamin Kl injection only for the approved indication and in accordance to the dosage regimen as stated in the package insert. They were also advised to weigh against the risk and benefit before prescription and choose the suitable route and control the injection rate strictly. In addition, manufacturers were advised to include such adverse reactions in the package insert and promote the importance of appropriate use of drug clinically. They were advised to devise an effective risk management plan and monitor the adverse reactions actively.

In Hong Kong, there are five registered injection containing vitamin Kl. They are used for bleeding disorders caused by vitamin K deficiency, severe hypoprothrombinaemia or overdose with anticoagulant. Their package inserts have stated that it is contraindicated for patients with hypersensitivity to the drug. In view of SFDA's recommendation, a letter to healthcare professionals was issued on 28 December 2011. DH will keep vigilant against any updated safety news of the drug.

Singapore: Reports of lymphadenitis following administration of BCG Vaccine SSI

On 27 December 2011, HSA of Singapore updated healthcare professionals on the suspected reports of lymphadenitis following the administration of the

Safety Update

Bacillus Calmette- Guérin (BCG) Vaccine Staten Serum Institute (SSI). It is the sole BCG vaccine registered in Singapore since June 2003 and is routinely given to newborns as part of the National Childhood Immunization Schedule. The observation arose from the active surveillance and monitoring of vaccine adverse events (VAE) at one of the local hospitals.

From January to October 2011, HSA received a total of 53 reports of lymphadenitis, out of which 27 cases presented as suppurative lymphadenitis. The number of cases was found to be higher than those reported in 2010 (25 reports of lymphadenitis with 16 cases were suppurative). The increase in number of suppurative lymphadenitis may possibly attributed to the additional review of paediatric referrals with mycobacterial infections at the new specialist outpatient clinic at KK Women's and Children's Hospital. The rising trend was also identifed in some countries such as Ireland and Latvia in recent years but their overall rate and pattern remained consistent with the expected frequency as listed in the package insert of the vaccine. The incidence of suppurative lymphadenitis observed in Singapore in 2011 was also found to be comparable to background incidences reported in literature. Studies revealed that the occurrence of suppurative lymphadenitis depended on many factors including the strain of BCG vaccine and its constituents (risk increased with the number of colony-forming units), host-related factors (risk inceased among patients in serious immunodeficiency states) as well as administration techniques (risk of inadvertent subcutaneous injection increased for vaccination among infants aged under six months). The median duration of symptoms prior to patient's presentation was two months.

In Hong Kong, BCG Vaccine SSI Powder for Inj 0.75mg/ml (HK-44952) is registered by Mekim Ltd. and manufactured by Staten Serum Institute in Denmark. It is a prescription medicine used for immunisation against tuberculosis and is part of the Hong Kong Childhood Immuisation Programme. Review of local data from discharge diagnosis of Hospital Authority up to June 2011 revealed that the incidence of reported suppurative lymphadenitis during 2009 – 2010 was 2.13 cases per 10,000 doses which is within the range of figures cited by the WHO of 1 to 10 per 10,000 doses. In view of HSA's recommendation, a letter to healthcare professionals was issued on 28 December 2011. DH will keep vigilant against any updated safety news of the drug.

Drug Recall

Batch recall of Omnaris Nasal Spray 50mcg HK-59322)

On 16 November 2011, DH endorsed the voluntary recall of one batch of Omnaris Nasal Spray 50mcg (Omnaris) (batch number: 137930) from shelves by a licensed drug wholesaler, Nycomed (Hong Kong) Limited (Nycomed), in view of a quality defect. Omnaris is a prescription medicine containing ciclesonide which is a steroid indicated for treatment of nasal symptoms associated with allergic rhinitis.

DH received notification from the company that the product's German manufacturer, Nycomed Gmbh, conducted a worldwide recall of the affected batch as the manufacturer discovered pinhole or leakage in some of the pouches which might affect the product quality. According to the manufacturer, the defects in the pouches might lead to oxygen ingress to the pouch from ambient air and lead to a decrease of the preservative and an increase of its degradation product. The affected batch was manufactured in August 2010. A total of 9,807 boxes were imported to Hong Kong and supplied to hospitals under the Hospital Authority (HA), private hospitals, private doctors, pharmacies and exported to Macao. According to the information from Nycomed so far, no batches manufactured since January 2011 showed pinhole defects of the pouches.

DH had alerted HA, private hospitals, professional healthcare bodies and the Macao authority about the matter and closely monitored the recall. DH had not received any related adverse reports. Press statement was released on the same day.

Batch recall of Glupozide 80mg tablets (HK-48195)

On 28 November 2011, DH instructed a licensed drug manufacturer, APT Pharma Limited (APT), to recall a batch (batch number: H00406) of Glupozide 80mg tablets in view of a quality defect. The defect

was identified by the DH during investigation of a public complaint which confirmed the finding of a suspected plastic fragment embedded in one of the above tablets. Glupozide is a prescription medicine containing gliclazide which is used for the control of blood glucose in diabetic patients.

According to APT, the tablets were usually manufactured by APT Pharma (China) Co Ltd in Guangdong and then exported to Hong Kong for packaging by APT. The affected batch was manufactured in June 2011. A total of 2,255 boxes of 500 tablets were supplied to various HA hospitals. That was an isolated detection, with no indication that other batches were affected nor any other report of relevant adverse incident was received.

DH had alerted HA and the Guangdong drug regulatory authority on the matter and closely monitored the recall. Press statement was released on the same day.

Batch recall of Eye Mo 36 Eye Drop 0.05% (HK-16622)

On 28 November 2011, DH endorsed the voluntary recall of a batch (batch number: X012FA-1) of Eye Mo 36 Eye Drops 0.05% from consumers by the licensed drug wholesaler, GlaxoSmithKline Limited (GSK), in view of a quality defect - the presence of fine crystals on the bottle. Eye Mo 36 is an over-the-counter medicine for soothing eye redness and irritation.

The company notified DH that it found the defect when investigating a consumer's enquiry about fine crystals found around the nozzle area of the product. GSK came to confirm the crystals as boric acid deposits, with the acid being an excipient used as a pH buffering agent in the product. GSK postulates that the crystal formation might be due to improper temperature or pressure encountered during air shipment of the particular batch. It was the only one batch dispatched by air, with all others was sent in by sea. GSK stressed that the recall was on a precautionary basis.

Eye Mo 36 was manufactured in Indonesia by PT Sterling Products Indonesia. According to GSK, around 31,500 bottles of the affected batch were imported into Hong Kong for supply to local pharmacies as well as medicine companies, with some re-exported to Macao.

Press statement was released on the same day. DH closely monitored the recall and no relevant adverse report had been received.

Members of the public were advised to consult their healthcare providers if they were in doubt or felt unwell after using the above products.

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

Recall of Marsedyl Elixir (HK-21197) and Prophenin Elixir (HK-32517)

On 24 November 2011, DH instructed a licensed drug manufacturer, Marching Pharmaceutical Ltd (Marching), to recall two products namely Marsedyl Elixir and Prophenin Elixir from the market because the company was found to have changed the shelf-life of both products from two years to six months during routine DH inspection. Since the change was not officially approved, the products were unregistered and recalled.

Both Marsedyl Elixir and Prophenin Elixir have the same formulation containing promethazine, codeine and ephedrine. They are used for the symptomatic treatment of cough and cold. They can only be sold under the supervision of pharmacists at registered pharmacies.

According to the records of Marching, about 400,000 bottles of the two products were supplied to local pharmacies. DH closely monitored the recall and press statement was released on the same day.

Pharmacies were advised to stop supplying the said products to clients. Members of the public who took the above medicines were advised to stop taking them and seek advice from healthcare professionals when in doubt.

Selling unregistered pharmaceutical products is an offence under the Pharmacy and Poisons Ordinance. The maximum penalty is a fine of $100,000 and two years' imprisonment.

Recall of Vidaza injection (HK-55407) and Eraxis for inj (HK-57097)

On 23 November and 12 December 2011, DH instructed the recall of an imported cancer drug Vidaza for Inj. 100mg and one batch of imported antifungal drug Eraxis for Inj 100mg respectively in response to the shortcomings found in the quality management system of Ben Venue Laboratories' (BVL) manufacturing site in Ohio, United States (US). On 23 November 2011, DH identified 13 registered pharmaceutical products manufactured by Ben Venue, including Vidaza and Eraxis.

Vidaza was manufactured by BVL and Baxter Oncology GmbH in Germany. As the problem affected BVL, only Vidaza manufactured by BVL was recalled on 23 November 2011. The product was imported by Jacobson Medical (Hong Kong) Limited (Jacobson), a licensed drug wholesaler. The record showed that a total of 1,144 vials had been imported into Hong Kong in 2011. They were distributed to HA, private hospitals, private practitioners and pharmacies.

As for Eraxis, the product registration certificate holder of Eraxis, Pfizer Corporation Hong Kong Limited (Pfizer) claimed that Eraxis manufactured by BVL was not marketed in Hong Kong on 23 November 2011. After the EMA recommended a precautionary recall of Eraxis (known as Ecalta outside Hong Kong) on 12 December 2011 as a result of the continuing review of the shortcomings in quality assurance identified in BVL, DH was informed by Pfizer that afternoon that they had in fact imported a batch of Eraxis (batch number: 0A7H5) in February 2010. Recall of Eraxis was then instructed immediately. A total of 2,000 boxes of Eraxis had been distributed to HA, private hospitals, and also exported to Macao and other countries. The expiry date was January 2012. There is another registered product, namely "Eraxis Powder for injection 100mg" (HK-59270), manufactured by Pharmacia & Upjohn Company in US, available in Hong Kong which is not affected by the current recall exercise.

No adverse reaction reports related to the two drugs were received. DH had issued press statements and letters to healthcare professionals, HA, private hospitals and healthcare professional bodies on both days of recall to alert them of the incidents. DH closely monitored the recalls.

Recall of three Nutriflex Lipid products of B. Bruan

On 21 December 2011, DH endorsed a licensed drug wholesaler, B. Braun Medical (H.K.) Limited (B.Braun) to recall from the market three Nutriflex Lipid products used for parenteral nutrition therapy because of potential particulate formation in the products.

DH received notification from B. Braun of the global recall of "Nutriflex Lipid Peri Emulsion for Infusion" (HK-50080), "Nutriflex Lipid Plus Emulsion for Infusion" (HK-50081) and "Nutriflex Lipid Special Emulsion for Infusion" (HK-50103) manufactured in its German manufacturer, B. Braun Melsungen AG. According to the information provided by B. Braun, the recall was initiated because the stability testing on the above products had identified potential particulate formation over time. Initial findings indicated that the cause could be due to a failure in the production line and the process of the production of the empty bags, which held the product.

According to the company, the affected products were imported and supplied to public and private hospitals, veterinary clinics and exported to Macao.

No adverse reports in relation to the products were received. DH alerted the HA, private hospitals and professional healthcare bodies about the matter and released a press statement on the same day. Healthcare professionals were advised to stop using the products and monitor their patients for adverse events. DH closely monitored the recall.

Batch recall of Xeloda tablet (HK-46234)

On 28 December 2011, DH endorsed the recall of a batch of cancer medicine, Xeloda Tab 500mg (batch number: X0106B01), by a licensed drug wholesaler, Roche Hong Kong Limited (Roche), because of improper preparation of the single active ingredient. Xeloda Tab 500mg is a prescription medicine for the treatment of colorectal, breast and gastric cancer. DH received notification from Roche that it was recalling globally two batches of Xeloda Tab 500mg (batch number: X0105 and X0106) because the review of batch records suggested a batch of active ingredient, capecitabine, could have been prepared

Drug Recall

by an unvalidated process. Since the quality of the product could not be ascertained, a recall was initiated as a precautionary measure.

The ingredient was manufactured in Roche facility in US. According to the available information, the issue affected one batch of Xeloda imported into Hong Kong. A total of 35 boxes of the affected batch had been supplied to local private hospitals, private doctors and pharmacies. Another 162 boxes were exported to Macao. DH had notified the involved hospitals, private doctors and pharmacies, as well as Macao health authority. Press statement was released and no adverse event report related to the drug was received. DH closely monitored the recall.

Drug Incident

Warning on orally consumed products for lowering blood glucose containing banned and undeclared drug ingredients

During the period between mid November 2011 and end December 2011, DH received notifications from HA about two patients feeling unwell after consumption of orally consumed products for lowering blood glucose. Banned and/or undeclared drug ingredients were detected in these products by the Government laboratory. They obtained their products outside Hong Kong. The details of the cases were listed as follows.

Patient	Products consumed	Symptoms developed	Drug ingredients detected in laboratory test
84-year old man	Jin Yu Tang Tai Han Kang Pai Pu Ling Jiao Nang (金禦唐肽含康牌葡靈膠囊)	Hip pain	Metformin, Rosiglitazone, Glibenclamide, Phenolphthalein
67-year old man	Tangren 365 (糖人 365 康巽牌桑葛活胰素膠囊)	Dizziness and chest discomfort	Phenformin, Rosiglitazone, Glimepiride, Hydrochlorothiazide

Metformin, rosiglitazone, glibenclamide and glimepiride are western drug ingredients used for management of diabetes. Their side effects include anorexia, nausea, vomiting, diarrhea and lactic acidosis for metformin; headache, dizziness, and lower limb oedema for rosiglitazone; nausea and gastro-intestinal upset for glibenclamide and glimepiride.

Rosiglitazone should not be used in those with a history of heart failure.

Hydrochlorothiazide is a western drug ingredient used for management of hypertension. Its side effects include hypotension, electrolyte imbalance and gastro-intestinal upset.

Phenformin is also a hypoglycaemic agent, but it had been banned in Hong Kong since 1985 because of the possible fatal effect of lactic acidosis.

Phenolphthalein was once used for treating constipation but had been banned for its cancer-causing effect.

Metformin, rosiglitazone, glibenclamide, glimepiride and hydrochlorothiazide are all Part I poisons. Under the Pharmacy and Poisons Ordinance, products containing them can only be sold with a doctor's prescription and under the supervision of a pharmacist.

Patients with chronic medical illness which requires holistic long term management were advised to consult healthcare professionals for appropriate advice on medication. They were strongly urged not to self-medicate or use over-the-counter medication without professional supervision. People who had taken the above products were advised to consult their healthcare providers immediately because they might cause life-threatening hypoglycemia and lactic acidosis.

Press statements related to these two cases were issued.

Drug Incident

Warning on slimming product found with banned drug ingredients

On 20 December 2011, DH issued press statement to appeal the public not to buy or consume a slimming product called "Xian Zhe Su Jiao Nang" (which bears the words "Chang Qing Chun" on its capsules 「纖之素膠囊」(膠囊上標示「常青春」字樣) as it was found to contain undeclared drug ingredients that might cause serious side effects.

DH was notified by the HA about a 20-year-old lady who was hospitalized on December 10, 2011 because of hand tremors and substantial weight loss. She described a history of consumption of the above slimming product. The product was purchased in the Mainland by the patient's friend. The HA's laboratory test on the product sample showed the presence of animal thyroid tissue, sibutramine, phenolphthalein and fenfluramine. She was discharged against medical advice on December 13, 2011 after treatment.

Both sibutramine and fenfluramine are Part I poisons and were once western medicines used as appetite suppressants. Since November 2010, products containing sibutramine had been banned because of increased cardiovascular risk. Fenfluramine was banned from the market on January 1998 because it may cause pulmonary hypertension and valvular heart diseases. Phenolphthalein was once used for treating constipation but had been banned on January 2001 for its cancer-causing effect. Animal thyroid tissue is not an appropriate agent for weight reduction.

Public were advised to control weight through good diet and appropriate exercise. They were advised to consult healthcare professionals before using any medication for weight control.

Persons arrested for selling unregistered pharmaceutical products

On 12 December and 30 December 2011, joint operations were conducted by DH and the Police resulting in the arrests of a 26-year-old man for suspected illegal sale of one box of motion sickness pills, and a 43-year-old woman for suspected illegal sale of one bottle of Careprost. DH issued press statements on the days of operations.

For the former case, intelligent was received alleging an unregistered medicine claimed for treating motion sickness was sold on the Internet. Investigation revealed that the product had never been imported nor registered in Hong Kong. The product contained the drug ingredients scopolamine (a Part I poison) and pheniramine (a Part II poison). Both scopolamine and pheniramine are used for the relief of motion sickness. Side effects include drowsiness and fatigue.

For the latter case, it was discovered through DH's surveillance programme that Careprost, which was claimed to increase eyelashes growth, was sold on the Internet. Careprost contained bimatoprost (a Part I poison), which is indicated for the treatment of open-angle glaucoma and ocular hypertension, as well as for the treatment of eyelashes hypotrichosis (a condition of inadequate amount of eyelashes). Side effects include eye irritation, inflammation of eyelids, cataract, redness of eye, and headaches.

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 such as scopolamine and bimatoprost must not be sold on Internet. They must be sold at registered pharmacy by a registered pharmacist or under his or her supervision. In addition, products containing bimatoprost can only be sold with a doctor's prescription. Sale and possession of unregistered pharmaceutical product and Part I poison is a contravention of the Ordinance and the maximum penalty for each offence is $100,000 fine and two years' imprisonment.

DH appealed to members of the public not to sell or use products of unknown or doubtful composition from the market or the Internet as unregistered pharmaceutical products have not been evaluated by the Pharmacy and Poisons Board, their product safety, quality and efficacy may not be guaranteed. They were advised to stop using the product immediately and consult healthcare professionals for advice if they feel unwell after taking the concerned product.

Useful Contact

Drug Complaint:

Tel: 2572 2068

Fax: 2147 0457 & 2123 1996

E-mail: pharmgeneral@dh.gov.hk

Adverse Drug Reaction (ADR) Reporting:

You are encouraged to report any suspected or confirmed ADR cases to our office by:

Tel: 2319 2920

Fax: 2147 0457

E-mail: adr@dh.gov.hk

Post: ***Pharmacovigilance Unit,***
Drug Office, Department of Health,
3/F, Public Health Laboratory Centre,
382 Nam Cheong Street, Kowloon

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