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HSA Health Sciences Authority

ADVERSE DRUG REACTION NEWS

Contents

POTENTIAL RISK OF NEW PRIMARY MALIGNANCY WITH XGEVA®

Key Points

- A pooled safety analysis of four Phase III studies showed a small increased rate of new primary malignancy (NPM) in patients with advanced malignancies treated with Xgeva® (denosumab) compared to zoledronic acid
- Although a clear causal mechanism has not been identified, a contributory role of Xgeva® in the development of the NPM could not be excluded
- Healthcare professionals are encouraged to take into consideration the potential increased risk of NPM, when assessing the benefit-risk of Xgeva® therapy for their patients

HSA would like to inform healthcare professionals about a pooled safety analysis which showed an increased rate of new primary malignancy (NPM) in patients with advanced malignancies treated with Xgeva® (denosumab) compared to zoledronic acid. However, the incidence and event rates for any NPM were low and the absolute difference in event rates were small. No treatment-related pattern in individual cancers or cancer groupings was apparent.

Xgeva® (Amgen Singapore Manufacturing Pte. Ltd.) is a human monoclonal antibody (IgG2) that has been registered in Singapore since March 2012. It is indicated for the prevention of skeletal related events (e.g. pathological fracture, spinal cord compression) in adults with bone metastases from solid tumour, as well as the treatment of adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity.

Xgeva® targets and binds with high affinity and specificity to the receptor activator of nuclear factor kappa-B ligand (RANKL), a membrane protein essential for the formation, function and survival of osteoclasts. The binding of Xgeva® with RANKL interferes with the RANKL and RANK receptor signalling pathway, thereby decreasing bone resorption and cancer-induced bone destruction.

Influence of RANK modulation on the immune system[1, 2]

The RANKL/RANK signalling pathway regulates diverse physiological functions and organ development in the body. Besides its role in the regulation of bone homeostasis, the inhibition of the RANKL/RANK signalling pathway has also been hypothesised to play a role in immune modulation. RANK and RANKL are expressed on a variety of immune cells, such as dendritic cells, monocytes, and both T and B lymphocytes. The RANKL has been shown to play a role in preventing apoptosis in monocytes and dendritic cells, as well as in activating the antigen-presenting functions of monocytes to T cells. Hence, it has been postulated that inhibition of the RANK/RANKL signalling pathway might potentially lead to impairment of immune surveillance mechanisms, thereby predisposing susceptible patients to an increased risk of malignancy.

Review by the European Medicines Agency[3,4]

During a routine review of Xgeva® safety data in February 2018, the European Medicines Agency (EMA) noted that NPM was reported more frequently in patients with advanced malignancies involving bone treated with Xgeva® (120mg once monthly) compared to zoledronic acid (4mg once monthly). In a pooled analysis of four Phase 3 studies that used zoledronic acid as a comparator, NPM occurred in 54 (1.5%) of 3,691 patients treated with Xgeva® (median exposure: 13.8 months; range: 1.0 to 51.7 months), and in 33 (0.9%) of 3,688 patients treated with zoledronic acid (median exposure: 12.9 months; range: 1.0 to 50.8 months) (risk ratio: 1.64, 95% CI 1.07-2.52). The cumulative incidence at one year was 1.1% for Xgeva® and 0.6% for zoledronic acid.

Review of the available information did not identify any treatment-related pattern in individual cancers or cancer groupings. Although the absolute differences in event rates were small, and a clear causal mechanism has not been identified, the EMA considered that

the involvement of Xgeva® and a potential mechanism related to impaired immune surveillance could not be excluded. Consequently, the European Union (EU) product information for Xgeva® was updated to include information about the imbalance in NPM observed from clinical studies. A Dear Healthcare Professional Letter was also issued in the EU to inform healthcare professionals about this potential risk.

Local situation and HSA's advisory

To date, HSA has not received any local adverse event report of NPM associated with the use of Xgeva®. The Singapore package insert for Xgeva® is in the process of being updated to include information about the incidence of NPM reported from the pooled safety analysis. Healthcare professionals are encouraged to take into consideration the above safety information when assessing the benefit-risk of Xgeva® therapy for their patients.

References

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4. *https://assets.publishing.service.gov.uk/media/5b2ccd01ed915d587f69eec5/Xgeva-DHPC-1605_signed.pdf*

EARLY TERMINATION OF ALLOZITHRO TRIAL DUE TO INCREASED RISK OF RELAPSE IN HAEMATOPOIETIC STEM CELL TRANSPLANTATION PATIENTS TREATED WITH AZITHROMYCIN FOR PROPHYLAXIS OF BRONCHIOLITIS OBLITERANS SYNDROME

Key Points

- A clinical trial, ALLOZITHRO, which investigated the effectiveness of long-term azithromycin exposure to prevent bronchiolitis obliterans syndrome (BOS) in patients who underwent allogeneic haematopoietic stem cell transplantation (HSCT) was prematurely terminated after an increased risk of relapses was seen in patients taking azithromycin compared with placebo
- Locally, azithromycin is not approved for the prophylaxis of BOS in patients undergoing HSCT
- In view of the significant risk associated with the off-label use of azithromycin in HSCT patients for prophylaxis of BOS, healthcare professionals should take into consideration the findings from the ALLOZITHRO trial in the clinical management of their patients

HSA would like to alert healthcare professionals to the findings from a clinical trial, ALLOZITHRO, which investigated the effectiveness of long-term azithromycin to prevent BOS in patients with haematological malignancy who underwent allogeneic HSCT.[1] The trial was prematurely terminated after an increased rate of relapses of haematological malignancies and mortality was seen in patients taking azithromycin compared with placebo. Locally, azithromycin is not approved for the prophylaxis of BOS in patients undergoing HSCT. It is also not approved for this indication in other countries such as the United States and in the European Union.

Bronchiolitis obliterans syndrome

BOS is a serious complication associated with chronic graft-versus-host disease that may occur after allogeneic HSCT. It is a type of obstructive lung disease, characterised by fibrosis of bronchioles that results in progressive and irreversible airway obstruction. BOS typically develops within two years of the HSCT and is associated with significant mortality and morbidity.

Findings from the ALLOZITHRO trial

The ALLOZITHRO trial was a randomised, double-blind, placebo-controlled, phase 3 trial conducted in 19 French academic transplant centres. Its aim was to investigate if early administration of azithromycin could improve airflow decline-free survival two years after allogeneic HSCT. The trial enrolled 480 patients who were at least 16 years old and had undergone allogeneic HSCT due to haematological malignancy. They were randomised to receive azithromycin 250mg (n=243) or placebo (n=237) three times a week for two years, starting from the day of the pre-transplant conditioning regimen.

In September 2016, at 13 months after completing enrolment, the Data and Safety Monitoring Board detected an unanticipated imbalance across blinded groups in the number of haematological relapses, which occurred in 77 patients (32.9%) on azithromycin treatment compared to 48 patients (20.8%) on placebo (Adjusted hazard ratio [HR] 1.6 [95% CI, 1.1-2.3]). Patients in the azithromycin group also had a lower two-year survival rate (56.6%) compared to those receiving a placebo (70.1%) (Unadjusted HR 1.5 [95% CI, 1.1-2.0]). This led to the early termination of the trial in December 2016.

The trial investigators concluded that early administration of azithromycin for prophylaxis of BOS in HSCT patients resulted in worse airflow decline-free survival than did placebo. However, these findings were limited by the early termination of the trial and further investigation into the harm related to the relapses was required.

Local situation and HSA's advisory

Azithromycin, a macrolide antibiotic, is not approved for the prophylaxis of BOS in patients undergoing HSCT. Apart from Zithromax™ (Pfizer Pte Ltd) that has been registered locally since 1994, there are 14 other generic azithromycin-containing products registered in Singapore.

In September 2018, a Dear Healthcare Professional Letter was issued by Pfizer to inform healthcare professionals about the findings from the ALLOZITHRO trial.[2] The letter stated that evidence from the trial was considered strong enough to assume that long-term exposure to azithromycin following HSCT might be associated with an increased relapse risk of haematological malignancies and mortality, which outweighed its anticipated benefits for this off-label use. However, Pfizer's analysis of all relevant available data did not suggest that this risk applied to the approved indications of azithromycin or other patient populations.

In view of the significant risk associated with off-label use of azithromycin in HSCT patients for prophylaxis of BOS, healthcare professionals should take into consideration the above information in the clinical management of their patients.

References

1. *JAMA 2017; 318: 557-66*
2. *http://www.hsa.gov.sg/DHCPL*

ADVERSE EVENT REPORTS OF LIVER INJURY SUSPECTED WITH THE USE OF MAHOGANY SEEDS

Mahogany seeds are also known as *Swietenia macrophylla* seeds. The fruit of the mahogany seeds is commonly known as "Sky fruit" or "Buah Tunjuk Langit" (in Malay) or "向天果" (in Chinese). Mahogany seeds are used traditionally in Malaysia and other countries for the regulation of blood sugar and cardiovascular health.[1] Based on a review of the existing literature and monograph, there is a lack of efficacy and safety data on the use of mahogany seeds.[1]

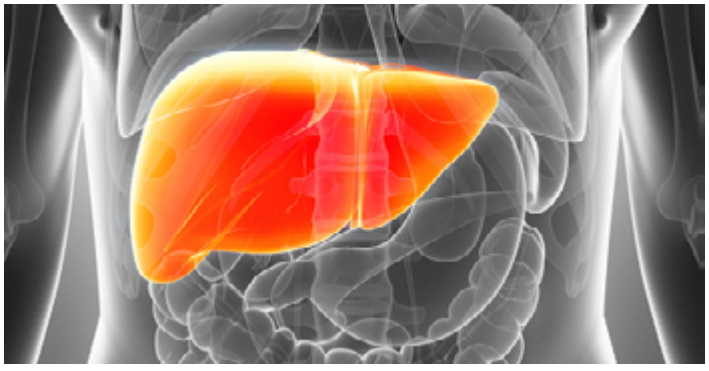
Since 2015 till October 2018, HSA has received seven* adverse event (AE) reports of liver injury suspected with the use of mahogany seeds.

Local AE reports of liver injury

The liver injuries reported were of varying severity, including transaminitis, jaundice and liver failure. The pattern of liver toxicity was either hepatocellular or mixed (hepatocellular and cholestatic). The age of the patients reported in the seven cases ranged from the 40s to 70s. The liver injury occurred between 30 to 45 days after consumption of the mahogany seeds except in one patient, where the onset duration of the AE was six months. Five of the patients consumed the seeds in its raw form ranging from ten seeds a month to 18 seeds daily, while the remaining two consumed mahogany seeds formulated in a capsule. Of the two brands of capsules, one was labelled as 'Natural Miracle Healer' while the other was an unknown brand. The patients consumed mahogany seeds for the purpose of controlling their diabetes, hypertension and/or general well-being.

Six patients had underlying medical conditions including diabetes, hypertension, hyperlipidaemia and fatty liver and five of them were taking concomitant medicines.

Five of the patients were hospitalised. Other than liver injuries, some patients also presented with other AEs including acute kidney injury, polyarthralgia and mesenteric panniculitis. All patients were reported to have recovered or were recovering after stopping the use of the products.



Conclusion

HSA's investigations into the causality of the liver toxicity are ongoing. Based on a literature review, there is lack of scientific data on the risk of liver injury and mahogany seeds. HSA will continue to closely monitor the situation to better understand this safety concern.

Healthcare professionals are encouraged to ask their patients about the use of mahogany seeds and other complementary products when taking medication history and report suspected cases to the Vigilance and Compliance Branch of HSA.

* Three of the reports were published in references 2 and 3.

References

1. *http://www. globinmed.com/index.php?option=com_content&view=article&id=83145:swietenia-*
2. *Yeap V. et. al. Liver failure associated with mahogany seed extract consumption, BMJ Case Report 2018.*
3. *Leong W.Y., et. al. Consumption of Swietenia macrophylla seeds can lead to hepatitis and autoimmune phenomena. Rheumatology Advances in Practice 2018; 2.*

Figure 1. Mahogany seeds

Figure 2. 'Natural Miracle Healer'

HIGHLIGHTS ON DRUG-ADVERSE EVENT PAIRS OF INTEREST REVIEWED BY HSA FOR THE YEAR 2018

All spontaneous adverse event (AE) reports received by HSA are reviewed daily. The review is done on the individual case reports where drug-AE pairs of interest are subsequently analysed at an aggregated level.

The table below presents case information on selected drug-AE pairs that HSA would like to highlight based on the cumulative spontaneous reports received till September 2018. HSA will continue to monitor any international developments and local AE reports regarding these drug-AE pairs and inform healthcare professionals of any new significant findings.

Drug-AE Pair	Description of cases	Highlighted Information
Cefepime and encephalopathy	To date, HSA has received eight suspected reports (of which, two were reported in 2018). All the eight cases reported were in patients aged 60 and above. Cefepime was the only suspected drug in seven cases while haloperidol was reported as a co-suspect drug in one case. <u>Reports in 2018</u>: • The first case occurred in an elderly patient who developed encephalopathy after taking IV cefepime 2g twice a day for five days for osteomyelitis. The patient's baseline creatinine was 107 umol/L and he was taking statins, dual anti-platelet therapy and sitagliptin as concomitant medications. Subsequently, the patient passed away from hospital-acquired pneumonia. • The second case occurred in another elderly patient who developed encephalopathy after taking cefepime for osteomyelitis. However, the dose of cefepime that was given was not provided in the report. Patient's baseline creatinine level was 399 umol/L and he was taking antihypertensive medications and a statin.	A Dear Healthcare Professional Letter was issued by Bristol-Myers Squibb (Singapore) Pte. Ltd. in March 2018 to remind healthcare professionals on the importance of cefepime dosage adjustment in patients with renal impairment, including during treatment or as soon as the creatinine clearance is 50 ml/min or less. This is due to the risk of serious neurologic adverse events, including encephalopathy which have been reported mostly in patients with renal impairment who received dosages that exceeded the recommendations.[1] There are warnings on reversible encephalopathy (impaired consciousness with confusion, hallucinations, stupor and coma) in the local package inserts of cefepime. In most cases, those affected were patients with renal dysfunction who had received cefepime at dosages higher than those recommended. However, there were cases of encephalopathy that occurred in patients who received proper dosage adjustment according to their degree of renal impairment.[2]
DPP-4 inhibitors and bullous pemphigoid	To date, HSA has received four suspected reports (of which, three were reported in 2018). <u>Reports in 2018</u>: The three cases reported in 2018 involved patients who were above the age of 60 years old. Two cases were associated with linagliptin while one was associated with sitagliptin. In the case where sitagliptin was taken, the patient was hospitalised for the AE. There was a long latency of about 32 months after taking sitagliptin 25mg once daily for diabetes mellitus. The patient also had a past medical history of hypertension, hyperlipidemia, gastritis, chronic renal failure and prostate carcinoma.	There are warnings on bullous pemphigoid in the local package inserts of linagliptin[3] and sitagliptin[4]. It is stated in the package insert of sitagliptin that post-marketing cases of bullous pemphigoid requiring hospitalisation have been reported with DPP-4 inhibitor use. In the reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of DPP-4 inhibitor. Patients are advised to seek medical advice if they develop blisters or erosions while on DPP-4 inhibitors.
Linagliptin and arthralgia	To date, HSA has received three suspected reports (of which, two were reported in 2018). <u>Reports in 2018</u>: The two cases reported in 2018 involved elderly patients (>80 years old) with severe and disabling arthralgia associated with linagliptin. No other information was reported.	US FDA flagged out the safety issue of severe and disabling arthralgia associated with DPP-4 inhibitors in 2015.[5] HSA had conducted the risk assessment for this safety issue and the package inserts for sitagliptin, saxagliptin and vidagliptin had been updated on this potential risk. The time to onset of symptoms following DPP-4 inhibitor therapy ranged from one day to years and patients experienced relief of symptoms upon discontinuation of the medication. A subset of the patients had experienced a recurrence of their symptoms when restarting the same drug or a different DPP-4 inhibitor.[4]

Drug-AE Pair	Description of cases	Highlighted Information
SGLT2 inhibitors and liver disorders	To date, HSA has received six suspected reports (of which , two were reported in 2018). The age range for the six cases varied from 12 to 80 years old with the onset of the AE from 12 to 120 days. Patients were either taking canagliflozin (n=4) or dapagliflozin (n=2) and thereafter developed liver issues namely jaundice (n=1), elevated liver enzymes (n=4) or hepatitis (n=1). Two cases were reported to have underlying liver conditions (i.e. hepatitis, cirrhosis). Reports in 2018: • The first case occurred in a female patient in her 20s who has a medical history of type 2 diabetes mellitus (on metformin) with hypercholesterolemia. She was given canagliflozin for three months before presenting to the A&E with elevated liver enzymes. Canagliflozin was stopped and she was subsequently diagnosed with viral hepatitis and cholecystitis. She recovered from this episode. Although the doctor reported that the patient's elevated liver enzymes were likely due to viral hepatitis and cholecystitis, he did not rule out the possibility of canagliflozin contributing to the elevated liver enzymes. • The second case involved a patient who was started on dapagliflozin and subsequently experienced hepatitis. The patient recovered one month later.	Hepatotoxicity from canagliflozin, dapagliflozin and empagliflozin is rare and have not been associated with acute liver failure in multiple large randomised controlled trials. The lack of hepatotoxicity of SGLT-2 inhibitors may relate to their minimal hepatic metabolism which is largely via UDP-glucuronylsyltransferase.[6] Although liver issues are currently not listed as AEs in the package inserts of dapagliflozin and canagliflozin, it is listed in the empagliflozin[7] package insert which states that cases of hepatic injury have been reported in clinical trials although a causal relationship between empagliflozin and hepatic injury has not been established. 

HSA would like to thank healthcare professionals for their partnership in AE reporting. With continual vigilance in identifying serious AEs happening locally, regulatory actions may then be taken to mitigate the risks and help protect public health. We would also like to take this opportunity to highlight the importance of good quality reports with the relevant details to facilitate our causality assessments.

References

1. *https://www.hsa.gov.sg/content/hsa/en/Health_Products_Regulation/Safety_Information_and_Product_Recalls/Dear_Healthcare_Professional_Letters/2018/risk-of-serious-neurologicadverseeventsincludingencephalopathyas.html*
2. *Micromedex 2. Micromedex® 2.0 (electronic version). Truven Health Analytics, Greenwood Village, Colorado, USA. Available at: http://www.micromedexsolutions.com/. Last accessed on 20 Sept 2018*
3. *Singapore package insert for Trajenta®. Approved 19 April 2018.*
4. *Singapore package insert for Januvia™. Approved 5 March 2018.*
5. *https://www.fda.gov/Drugs/DrugSafety/ucm459579.htm*
6. *https://livertox.nih.gov/SGLT-2_Inhibitors.htm*
7. *Singapore package insert for Jardiance®. Approved 14 Feb 2018.*

USEFUL INFORMATION

Doctors, dentists and pharmacists can claim continuing education points for reading each issue of the HSA ADR News Bulletin. Doctors can apply for one non-core Continuing Medical Education (CME) point under category 3A, dentists can apply for one Continuing Professional Education (CPE) point under category 3A and pharmacists can apply for one patient-care Continuing Professional Education (CPE) point under category 3A per issue of the bulletin.

UPDATES ON ADULTERATED PRODUCTS USED FOR PAIN RELIEF REPORTED TO HSA

Key Points

- From 2013 to September 2018, the most common category of adulterated products detected through adverse event (AE) reporting by healthcare professionals is pain relief products.
- Careful medication history taking, including the consumption of complementary health products and other supplements is key in detecting potentially adulterated products
- Press releases were issued by HSA to alert the public against taking adulterated products and also published on HSA's website

From 2013 to September 2018, HSA received 81 AE reports from healthcare professionals which were suspected to be associated with the use of adulterated products. Sixty-seven percent of the reports involved adulterated products used for pain relief. The majority were steroid-related AEs such as Cushing's Syndrome, adrenal crisis, adrenal insufficiency, impaired glucose tolerance, hypercortisolism and weight gain. The most common adulterant detected was corticosteroids (73.9%) (e.g., dexamethasone, prednisolone and prednisone). Other adulterants detected were NSAIDS, diuretics, antihistamines and antibiotics. Press releases were issued on these products as part of HSA's ongoing efforts to educate consumers about the risk of adulterated products.

In 2018, HSA issued three press releases to alert the public on the following five adulterated products which were sold for pain relief.

'Herba Saraf'

'Herba Saraf' was reported by a polyclinic doctor who was suspicious of his patient's newly diagnosed impaired glucose tolerance. The patient, who was in her 40s, had no chronic medical condition. After careful medication history taking by the doctor, the patient revealed that she was taking a supplement for her knee pain. She had been taking it for more than a month and found it very effective in relieving pain. The product was obtained from a relative in Malaysia who had bought it online. The product was labelled to contain only herbal ingredients and claimed to relieve pain such as joint pain, gout, back pain, lethargy and migraine. The doctor's suspicion was raised and he promptly reported this case to HSA's Vigilance and Compliance Branch (VCB). After review and assessment by HSA, the product was sent to HSA's Pharmaceutical Laboratory for testing. The results showed that it contained dexamethasone.

Figure 1. Herba Saraf

'Ausbee Australia® Ausbee Herbal Powder Capsules'

A female patient in her 70s with underlying chronic medical conditions was admitted to the hospital after sustaining a fracture in the neck of her right femur. She underwent an emergency right hip hemiarthroplasty operation. On the first post-operation day, she experienced an adrenal crisis and severe hypotension which was refractory to fluid resuscitation and inotropic support. She was admitted into the Intensive Care Unit (ICU) and required intubation, high doses of inotropes and vasopressors. Upon interviewing the patient's family members, the anaesthetist found out that the patient had been taking a supplement 'Ausbee Australia® Ausbee Herbal Powder Capsules' for her back pain. This raised her suspicion that the product could have caused the post-operation complications and she reported it to HSA. The product was tested to contain dexamethasone, chloramphenicol, chlorpheniramine, ibuprofen and tetracycline.

Figure 2. Ausbee Australia® Ausbee Herbal Powder Capsules (Front)

Figure 3. Ausbee Australia® Ausbee Herbal Powder Capsules (Back)

'Shen Loon She™ Edoly Capsule'

A male patient in his 60s exhibited symptoms of Cushing's Syndrome such as thinning of skin, reddish purplish striae on his skin, elevated glucose levels and high blood pressure after taking 'Shen Loon She™ Edoly Capsule' for close to ten years for his joint pain. Upon consultation with a general practitioner (GP), the AEs were promptly reported to HSA. The patient claimed that he had obtained the product from Malaysia. Upon testing, the suspected product was found to contain dexamethasone and chlorpheniramine.

Figure 4. Shen Loon She™ Edoly Capsule (Front)

Figure 5. Shen Loon She™ Edoly Capsule (Side)

'Jus Al Sunnah Gold 1001 Khasiat Jus Alternatif' and 'Jus Al Sunnah 1001 Khasiat Jus Alternatif'

Five patients, including a child, developed serious steroid-induced AEs such as Cushing's syndrome and uncontrolled diabetes after consuming an adulterated juice called 'Jus Al Sunnah Gold 1001 Khasiat Just Alternatif'. HSA was alerted to the health risks associated with these products by a doctor from a public hospital and a GP. In addition, another variant under the same brand 'Jus Al Sunnah 1001 Khasiat Jus Alternatif' was detected and seized from the supplier. When the two variants were tested, both were found to contain dexamethasone and prednisolone. 'Jus Al Sunnah Gold 1001 Khasiat Jus Alternatif' was found to contain an additional adulterant, diclofenac.

Healthcare professionals play an important role in helping HSA detect adulterated products. A careful medication history taking, including the consumption of complementary health products and other supplements are beneficial in detecting potentially adulterated products.

Figure 6. Jus Al Sunnah Gold 1001 Khasiat Jus Alternatif (Front)

Figure 7. Jus Al Sunnah Gold 1001 Khasiat Jus Alternatif (Side)

Figure 8. Jus Al Sunnah 1001 Khasiat Jus Alternatif (Box)

Figure 9. Jus Al Sunnah 1001 Khasiat Jus Alternatif (Bottle)

Healthcare professionals are encouraged to visit the HSA website at https://www.hsa.gov.sg/content/hsa/en/News_Events/Press_Releases.html

Or scan the QR code for more details.

LIST OF DEAR HEALTHCARE PROFESSIONAL LETTERS ON SAFETY CONCERNS ISSUED BY HSA, PHARMACEUTICAL AND MEDICAL DEVICE COMPANIES (1 SEP 2018 TO 30 NOV 2018)

For details of the DHCPL, please log on to MOHAlert via your professional board's website.

Therapeutic products

*27 Aug 2018	**Tecentriq® (atezolizumab)** New safety concern of immune-related nephritis
*30 Aug 2018	**Flolan (epoprostenol)** Temporary availability of two different sterile diluents (pH12 and pH10.5)
10 Sep 2018	**Azithromycin** Increased rate of relapses of haematological malignancies and mortality in haematopoietic stem cell transplantation
9 Oct 2018	**Ozurdex® 700 micrograms intravitreal implant (dexamethasone)** Product recall of selected batches due to possible detachment of a single loose silicon particle from the needle sleeve during implant administration
12 Oct 2018	**Epilim® (valproate)** New restriction on the use of valproate during pregnancy
14 and 21 Nov 2018	**Hydrochlorothiazide** Cumulative dose-dependent association with non-melanoma skin cancer
15 Nov 2018	**Imovane (zopiclone) tablet 7.5mg** New restriction of indication to "short-term" treatment of insomnia and additional recommendations on the duration of treatment to promote the proper use of zopiclone and limit the risk of abuse and drug dependence

Medical devices

4 Sep 2018	**Medtronic HeartWare™ HVAD™ Controller units** Potential hairline crack at the power ports of the controller housing of selected units
10 Sep 2018	**CyPass® Micro-Stent** Voluntary recall of affected device following long-term safety study results on increased risk of endothelial cell loss
13 Sep 2018	**Endologix AFX® Endovascular AAA System** Update to the Instruction For Use regarding Type III endoleak rates and suggestions for patient management
18 Sep 2018	**Zenith Alpha™ Thoracic Endovascular Graft** Reminder on the intended use of device as it has been used off-label for thoracic aortic dissections
31 Oct 2018	**Covidien Parietex™ Composite Parastomal Mesh** Voluntary recall of selected lots following reports of failure identified several years after parastomal hernia repair using the modified Sugarbaker repair technique
8 Nov 2018	**Boston Scientific SQ-RX™ Model 1010 Pulse Generator** Elevated rate of latent battery malfunctions resulting in accelerated battery depletion and shortened replacement interval
16 Nov 2018	**ePTFE Small Beading Vascular Graft products** Risk of small graft tears during removal of beading material not according to Instructions For Use
23 Nov 2018	**Bard® Lifestream™ Balloon Expandable Vascular Covered Stent** Inclusion of clinical study results on restenosis rate in the Instructions For Use

*DHCPLs not published in September 2018 issue

WHO-UMC-HSA INTER-REGIONAL PHARMACOVIGILANCE TRAINING WORKSHOP 2018

The WHO-UMC-HSA Inter-Regional Pharmacovigilance (PV) Training Workshop which was conducted in Singapore in August 2018, was attended by 71 participants from the ASEAN and Asia-Pacific region (Bangladesh, Brunei, Cambodia, Indonesia, Laos, Myanmar, Philippines and Thailand). The event marks the fourth training collaboration between the World Health Organisation (WHO), the Uppsala Monitoring Centre (UMC) and HSA, with the previous workshops being conducted in 2010, 2012 and 2015. Co-organised with Duke NUS Center of Regulatory Excellence (CORE), the aim of the workshop was to equip participants with the necessary skills to further strengthen PV capabilities within the region. These objectives are aligned with WHO and UMC's continual drive to communicate the importance of drug safety and PV among countries. For the first time, the training was open to members of the industry.

The underlying theme of this year's training event was 'Partnerships to protect public health' and the event provided the opportunity and platform to allow participants from the regulatory authorities and industry to work together to strengthen drug safety.

Key topics covered

The training was conducted by a team of local and international experts in the field of drug safety and vaccines, including Dr Viola Macolic Sarinic from the WHO, Dr Ruth Savage and Mr Danielle Satori from the UMC, A/Prof Thoon Koh Cheng and Dr Yung Chee Fu from KK Women's and Children's Hospital and Dr Phillip Buchy from GSK (GlaxoSmithKline) Vaccines. Participants were given an in-depth session on how causality assessments are performed and the various pharmacovigilance tools. The sessions were followed by hands-on exercises to further enhance their understanding on these topics. There were two panel discussions - one on 'Challenges and opportunities in protecting public health' and the other on 'Future trends and challenges in pharmacovigilance' to encourage the sharing of ideas and best practices currently adopted by the organisations that the participants were from.

HSA presented on Singapore's regulatory requirements as well as initiatives such as the pharmacogenomics and data analytics initiatives which were designed to further enhance drug safety in Singapore. As communication is key to partnerships, co-operation and the implementation of regulatory activities, participants were introduced to some of the techniques used for stakeholder communications. Complementing the presentations on the use and development of vaccines by external stakeholders, HSA also briefed participants on its active surveillance sentinel site for the monitoring of vaccine adverse events programme. In the closing session, the industry participants were provided an update on the regulatory requirements for managing product defects and recalls, risk management plans for therapeutic products and medical advertisements.

HSA's CEO Dr. Mimi Choong giving the opening speech


Speakers and participants at the Pharmacovigilance workshop

Seated L to R: Assoc Prof Chan Cheng Leng (HSA), Dr. Ruth Savage (WHO), CEO Dr. Mimi Choong (HSA), Dr. Viola Macolic Sarinic (WHO), Mr Danielle Satori (WHO), Dr. Dorothy Toh (HSA). Back row: HSA Vigilance and Compliance Branch team

Please send your enquiries, comments and suggestions to:

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