



Interim update on risk of serious ketoacidosis associated with sodium-glucose cotransporter-2 (SGLT2) inhibitors



HSA would like to highlight overseas cases of diabetic ketoacidosis (DKA), ketoacidosis or ketosis that have been reported with sodium-glucose cotransporter-2 (SGLT2) inhibitors. Locally, HSA has also received three reports of DKA associated with SGLT2 inhibitors. HSA and several international regulatory agencies have embarked on the safety review of this potential signal of serious ketoacidosis with SGLT2 inhibitors in view of the local and international signals.

SGLT2 inhibitors are a new class of antidiabetic medication that works by increasing the renal excretion of glucose, thereby resulting in a reduction in plasma glucose concentration, independent of changes in insulin concentrations or peripheral insulin resistance.¹ Three SGLT2 inhibitors, namely canagliflozin (Invokana™, Johnson & Johnson Pte Ltd), dapagliflozin (Forxiga®, AstraZeneca Singapore Pte Ltd) and empagliflozin (Jardiance®, Boehringer Ingelheim Singapore Pte Ltd), have been registered locally since February 2014, April 2014 and December 2014, respectively. They are indicated as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes mellitus, as monotherapy, add-on combination therapy with other glucose-lowering agents including insulin, and/or initial combination therapy with metformin.

Overseas cases identified by international regulatory agencies

a) US Food and Drug Administration (FDA)

The US FDA issued a drug safety communication in May 2015 informing that it is investigating the risk of serious ketoacidosis associated with SGLT2 inhibitors.² The review was triggered by the identification of 20 cases of DKA, ketoacidosis or ketosis reported with SGLT2 inhibitors from the FDA Adverse Event Reporting System (FAERS) database from March 2013 through June 2014. A temporal association with SGLT2 inhibitor initiation was noted in all cases, with a median time-to-onset of two weeks (range 1 to 175 days). Of note was the atypical presentation of the DKA cases, in that glucose levels were only mildly elevated at less than 200mg/dL (or 11mmol/L) in some reports, as compared to glucose levels of greater than 250mg/dL (or 14mmol/L) typically seen in patients with type 1 diabetes. Half of the cases also did not identify a triggering factor for DKA. Upon the completion of its investigation, the US FDA will determine if changes are required in the labelling for this class of drugs.

b) European Medicines Agency (EMA)

In June 2015, the EMA highlighted that it has initiated a review to evaluate the risk of DKA associated with SGLT2 inhibitors at the request of the European Commission following identification of a safety signal.³ Using the search terms "DKA", "ketoacidosis" and "ketosis",

a search in the Eudravigilance database in May 2015 for SGLT2 inhibitors identified 96 cases associated with canagliflozin, 46 cases associated with dapagliflozin and five cases associated with empagliflozin.

c) Health Canada

Health Canada initiated a safety review of SGLT2 inhibitors and risk of ketoacidosis in June 2015.⁴ A preliminary search of Health Canada's adverse reaction database identified one report of DKA involving hospitalisation of a patient taking an SGLT2 inhibitor and other concomitant medications.

Local cases of DKA

HSA has been closely monitoring the safety profile of the SGLT2 inhibitors following their registration in Singapore. As of August 2015, HSA has received three local serious reports of DKA associated with SGLT2 inhibitors.

The first report involved a 60-year-old male patient who developed DKA after 43 days of canagliflozin therapy. His concomitant medications included insulin glargine, metformin, sitagliptin and thyroxine. Upon admission, his blood glucose level was 9.8mmol/L and his urine was positive for ketones (3+).

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Risk of pancreatitis associated with vemurafenib

Vemurafenib (Zelboraf®, Roche Singapore Pte Ltd) is a low molecular weight inhibitor of BRAF serine-threonine kinase. It has been registered locally since February 2013 for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma. This article highlights the overseas cases of pancreatitis that have been reported with the use of vemurafenib.

Review by overseas regulatory agencies

a) European Medicines Agency (EMA)

A signal relating to a possible association with vemurafenib in nine cases of pancreatitis retrieved from the EudraVigilance database was identified by the EMA during its routine signal detection activities. During its meeting in September 2012, EMA's Pharmacovigilance Risk Assessment Committee (PRAC) agreed that preliminary analysis of the nine cases provided sufficient information to warrant further analysis of the data.¹ Further to two cumulative reviews conducted by the company in 2013 and 2014, the European labelling for Zelboraf® was updated in 2015 to add the adverse reaction of pancreatitis reported with a frequency of uncommon (i.e. occurring in $\geq 1/1,000$ to $< 1/100$ patients).²

b) Health Canada

In February 2015, Health Canada concluded that there is evidence of an association between vemurafenib and the occurrence of pancreatitis, which may be due, in part, to the fact that the drug may stimulate the proliferation of cells leading to obstructive pancreatitis.³ The safety review was initiated following identification of 18 cases of vemurafenib-associated pancreatitis (including seven cases of acute



pancreatitis) in ongoing clinical trials. A total of 61 reports of pancreatitis were retrieved from different sources, including scientific literature, the company's clinical and safety databases, the World Health Organisation database, and Health Canada's Vigilance Programme. The association of pancreatitis with use of vemurafenib was assessed to be "possible" or "probable" in 10 of the 61 reports. The Canadian labelling for Zelboraf® was subsequently updated to include the risk of pancreatitis.

Local situation

To date, HSA has not received any adverse reaction report of pancreatitis associated with vemurafenib. The local package insert (PI) for Zelboraf® currently lists pancreatitis as an uncommon adverse drug reaction. In view of overseas safety signals, the local PI has been strengthened to include information on patient monitoring and detection of pancreatitis.

HSA's advisory

Healthcare professionals are advised to remain vigilant to the possible signs and symptoms of pancreatitis in patients who are prescribed vemurafenib, and to consider the possibility of pancreatitis in the event of unexplained abdominal pain.

References

- 1 http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2012/10/WC500133303.pdf
- 2 http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002409/human_med_001544.jsp&mid=WC0b01ac058001d124
- 3 <http://www.hc-sc.gc.ca/dhp-mps/medeff/reviews-exams/revurafenib-eng.php>

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Interim update on risk of serious ketoacidosis associated with sodium-glucose cotransporter-2 (SGLT2) inhibitors

The second report involved a 43-year-old female patient who developed DKA after 11 days of canagliflozin therapy and was subsequently hospitalised for three days. Her concomitant medication included metformin, which she had been compliant in taking for more than five years. Upon admission, the patient had normal serum creatinine without any medical history of infections. Her blood glucose level was 16.3mmol/L and ketones were detected in her urine (3+).

The third report involved a 60-year-old female patient who was newly diagnosed with diabetes. She was initially thought to have type 2 diabetes mellitus and started on oral therapy, but the diagnosis was later changed to late-onset type 1 diabetes mellitus. The patient developed DKA after 81 days of dapagliflozin therapy. Upon admission, her blood glucose level was 13.7mmol/L and her urine was positive for ketones.

HSA's actions and advisory

HSA is reviewing the current available information and seeking expert opinions from local clinicians on this risk to determine if there is a need for further regulatory actions. Dear Healthcare Professional Letters (DHCPLs) were issued by the three product licence holders in July 2015 to warn of serious and sometimes

life-threatening cases of DKA during treatment with SGLT2 inhibitors.

While HSA's review is ongoing, healthcare professionals are advised to remain vigilant to the signs and symptoms of DKA in patients who are prescribed SGLT2 inhibitors. Healthcare professionals are encouraged to counsel patients and caregivers on the symptoms of metabolic acidosis, such as tachypnea or hyperventilation, anorexia, abdominal pain, nausea, vomiting, lethargy or mental status changes, and the need to seek medical attention promptly upon experiencing such symptoms.

Healthcare professionals are also encouraged to report any adverse reactions suspected to be associated with the use of SGLT2 inhibitors to the Vigilance and Compliance Branch of HSA.

HSA will provide an update on the outcome of our review when it is completed.

References

- 1 <http://www.australianprescriber.com/magazine/37/11/14/6>
- 2 <http://www.fda.gov/Drugs/DrugSafety/ucm446845.htm>
- 3 http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2015/06/news_detail_002344.jsp&mid=WC0b01ac058004d5c1
- 4 <http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2015/53892a-eng.php>

Testosterone and risk of cardiovascular events

HSA would like to bring to the attention of healthcare professionals, the overseas signals of cardiovascular (CV) events that have been associated with the use of testosterone-containing products. Safety reviews conducted by international regulatory agencies have concluded that the signal of CV risk remains weak and further investigations by the manufacturers, such as the conduct of a well-designed clinical trial and close monitoring of these safety events, are necessary to confirm this risk.

Testosterone is a steroid hormone that plays a role in the development of androgenic and anabolic processes. It is mainly indicated for replacement therapy in males with primary and secondary hypogonadal disorders. Some of the testosterone-containing products are also indicated for osteoporosis caused by androgen deficiency, or for masculinisation in female to male transsexuals. Testosterone was first licensed locally in 1990, and there are currently seven testosterone-containing products in different dosage forms, ranging from oral capsules to subcutaneous implants: Andriol Testocaps® (MSD Pharma (Singapore) Pte Ltd), Androgel® (Orient Europharma Pte Ltd), Depo-Testosterone® (Pfizer Pte Ltd), HOM® (Blendforte Trading Co), Nebido® (Bayer (South East Asia) Pte Ltd), Sustanon® (A Menarini Singapore Pte Ltd), and Testosterone Implant® (MSD Pharma (Singapore) Pte Ltd).

International regulatory actions

a) US Food and Drug Administration (FDA)

In February 2014, the US FDA initiated a review on the CV risk in testosterone-treated men. This review was in response to findings from two published observational studies^{1,2} that suggested an increased risk of CV events (namely stroke, myocardial infarction [MI], and death) in men who were prescribed testosterone therapy. In September 2014, a joint meeting between the Bone, Reproductive and Urologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee was convened to discuss the CV findings associated with testosterone available from published observational and meta-analysis studies. The advisory committee members generally agreed that the signal of CV risk is weak due to conflicting evidence from the studies. However, in view that some studies had observed this signal, the US FDA concluded that there is a possible increased CV risk associated with testosterone use. Manufacturers of testosterone-containing products were required to update the US package insert (PI) on the possible increased risk of MI and stroke, and to conduct a well-designed clinical trial to confirm if this risk exists with testosterone use.³

In June 2014, the US FDA issued a separate communication informing that the US PI of all testosterone-containing products would need to be updated on general warnings regarding the risk of venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE). This PI update followed the identification of VTE events associated with testosterone use from the FDA Adverse Event Reporting System (FAERS) database.⁴

b) European Medicines Agency (EMA)

In October 2014, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) conducted a similar review on the risk of CV events associated with testosterone, which concluded that based on current available data, the evidence for this risk remains weak and inconclusive.⁵ However, the PI for all testosterone-containing medicines should be updated on the current available safety information, including warnings on the population that might be at increased risk of CV events. In addition, the manufacturers of testosterone-containing products were required to closely monitor the CV safety concerns, including VTE events, and to submit the discussion of these findings to EMA by March 2016.

c) Health Canada

Health Canada completed its review on the CV risk of testosterone in July 2014. Based on the current available evidence, Health Canada concluded that there is a possibility of CV risk with the use of testosterone.⁶ Accordingly, the Canadian PIs of testosterone-containing products were updated to include a warning on possible CV events, including MI, stroke, VTE, tachycardia and atrial fibrillation.

d) New Zealand Medsafe

Medsafe's Medicines Adverse Reactions Committee (MARC) convened a meeting in September 2014 to discuss the CV risk associated with testosterone use. The committee concluded that based on the current evidence, there is no significant statistical evidence to support an association between testosterone and MI, VTE, or stroke, and that longer-term, adequately powered, placebo-controlled clinical trials are required to investigate the risk of CV events with testosterone.⁷

HSA's actions and advisory

HSA has received one local ADR report of MI associated with the use of testosterone. No local ADR reports of VTE associated with the use of testosterone have been received.

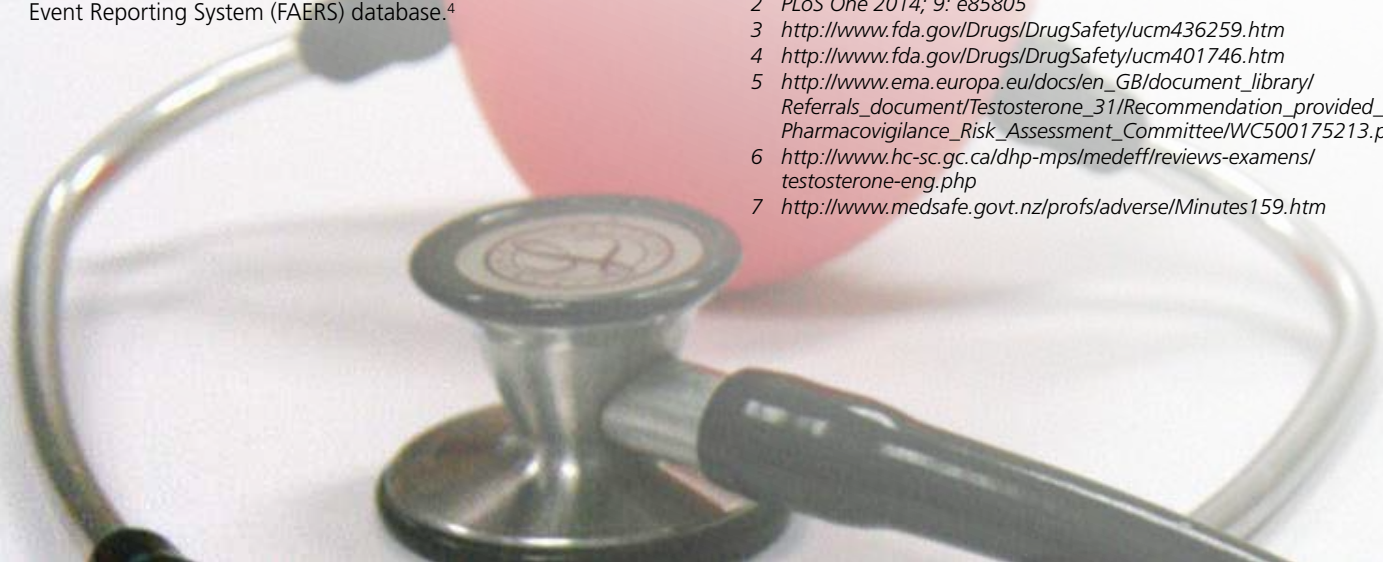
HSA has also consulted local experts (urologists and cardiologists) regarding the signal of CV risk with testosterone. Some of the experts were of the opinion that methodological limitations and biases may have impacted the findings of the observational studies mentioned above. HSA is working with the companies to ensure that the warnings and precautions relating to CV events are adequately highlighted across the PIs of testosterone-containing products.

HSA will continue to monitor international and local developments regarding the CV risk of testosterone-containing products and will update healthcare professionals of any new safety findings.

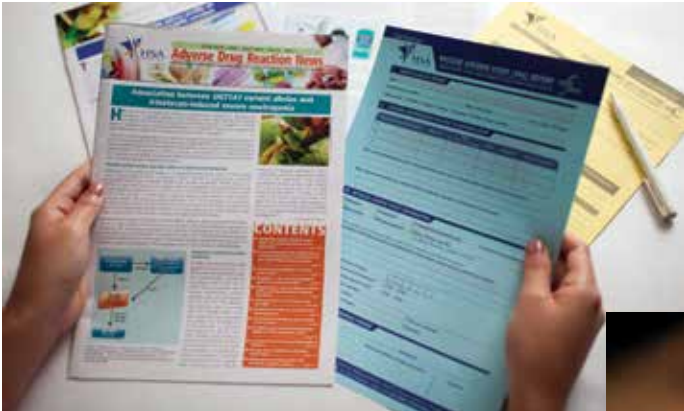
Healthcare professionals are advised to take into consideration the above safety issues when prescribing testosterone-containing products to their patients.

References

- 1 JAMA 2013; 310: 1829-36
- 2 PLoS One 2014; 9: e85805
- 3 <http://www.fda.gov/Drugs/DrugSafety/ucm436259.htm>
- 4 <http://www.fda.gov/Drugs/DrugSafety/ucm401746.htm>
- 5 http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Testosterone_31/Recommendation_provided_by_Pharmacovigilance_Risk_Assessment_Committee/WC500175213.pdf
- 6 <http://www.hc-sc.gc.ca/dhp-mps/medeff/reviews-examens/testosterone-eng.php>
- 7 <http://www.medsafe.govt.nz/profs/adverse/Minutes159.htm>



Partnership in vigilance: Reporting adverse events related to health products



The Vigilance and Compliance Branch monitors the safety of health products in Singapore through a number of post-marketing surveillance approaches. These include mandatory reporting of serious adverse events (AE) by pharmaceutical manufacturers, spontaneous reporting by healthcare professionals, literature reviews and the exchange of regulatory information with other national drug regulatory bodies. Among these approaches, spontaneous AE reporting by healthcare professionals forms the cornerstone of post-marketing health product safety surveillance. The AE Reporting Programme relies upon voluntary reporting of suspected AEs arising from the use of a health product (e.g., western drug, vaccine, biologics, complementary health product, cosmetics). Healthcare professionals are encouraged to notify HSA when they suspect there is a causal association between the health product taken and the AE experienced by the patient. Reporting an AE does not necessarily mean that there is a definite link between the event and the product.

AE reports, once submitted, are captured into our national database, which the Vigilance and Compliance Branch monitors for potential safety signals. Such findings can lead to regulatory actions such as updating of package inserts with relevant safety warnings and alerting healthcare professionals via advisories. For health products assessed to be associated with significant

safety issues that affect their overall benefit-risk profile but still remain beneficial for a selected group of patients, HSA may restrict the use of the affected health products so as to allow for their continued safe use in the local market while ensuring that adequate measures are in place to mitigate their risks.

HSA also contributes to the World Health Organisation (WHO) International Drug Monitoring Programme by submitting anonymised local AE reports to the WHO-Uppsala Monitoring Centre (UMC) in Sweden for international surveillance of adverse drug reactions. In the October 2014 issue of Uppsala Reports, the UMC reiterated the importance of both quantity in reporting and quality of individual case reports in making the WHO database a useful information resource.¹ The quality of reports submitted by national pharmacovigilance centres is gauged by the UMC using the completeness score, which is a measure of the amount of essential information available in a structured format for medical assessment. A high score corresponds to a well-documented case. Every country is encouraged to aim for both a high number of case reports per million inhabitants as well as a high completeness score on their reports.



Reporting of adverse events

Singapore has been ranked among the top countries with the highest number of AE reports submitted (based on per million inhabitants) to the WHO global surveillance database. However, further improvements can still be made in terms of the completeness of the reports submitted. To enhance the quality of the reports and aid in assessment of the cases, it is thus important that sufficient information be provided (where available).

General information to include in an AE reporting form, as well as the rationale for requesting them, are listed in Table 1. For all AE reports, the patient's and reporter's identities will be kept in strict confidence.

Table 1. General information to include in an AE report

Information required	Rationale
Patient's details Initials, gender, age/date of birth	To identify duplicate reports
Reporter's details Name, profession, place of practice, contact number, email address	To request for further information when needed or for follow-up on potential safety signals
Details of AE Date of onset/latency, concise description of AE (e.g., type of rash), severity	To assess causality and seriousness of AE
Suspected health product(s) Brand name or active ingredient(s), dose, indication, therapy dates, batch number*	Brand name (preferred): To determine brand-specific AEs Therapy dates: To establish temporal association Batch number: To assess batch-specific quality issues
Concomitant health product(s) including vaccines, complementary health products consumed at the same time and/or three months before the AE	To identify confounders or possible drug interactions
Other relevant information Pre-existing conditions, known allergies, pregnancies, laboratory tests done and results	To identify confounders
Seriousness of event and outcome Was the patient hospitalised due to the event? Recovery status, sequelae	To assess causality and seriousness of event
Treatment of AE Yes/No. If Yes, specify the treatment	

* Only for vaccine reports and/or where there are suspected quality defects

Azithromycin and drug reaction with eosinophilia and systemic symptoms (DRESS)

HSA would like to highlight to healthcare professionals overseas cases of drug reaction with eosinophilia and systemic symptoms (DRESS) associated with the use of azithromycin.

Azithromycin (Zithromax®, Pfizer Pte Ltd) is an azalide, a subclass of macrolide antibiotics that has been registered in Singapore since 1999 for the treatment of upper and lower respiratory tract infections and other infections involving susceptible organisms. It is also licensed under 11 other generic brands and is available under various dosage forms ranging from oral tablets to intravenous formulations.

DRESS is a severe drug reaction characterised by rash, fever, lymphadenopathy, and single or multiple organ involvement (e.g., liver, kidney) that typically occurs within eight weeks of drug initiation.¹ Haematologic abnormalities, including eosinophilia and atypical lymphocytosis, are also key characteristics of this syndrome.

Review by Health Canada²

In April 2014, Health Canada highlighted in its Canadian Adverse Reaction Newsletter that the package inserts (PI) for azithromycin-containing products have been updated with information on DRESS. This followed the receipt of a domestic report of DRESS suspected to be associated with azithromycin, as well as review of published literature on DRESS in patients treated with azithromycin.

The Canadian adverse reaction report described a 60-year-old female who experienced DRESS 18 days after taking azithromycin



to treat pharyngitis. Of the four DRESS cases that were published in literature,^{1,3-5} two cases involved children (aged two and eight) while the other two involved adults (aged 48 and 79). Two cases stated the time to onset, which was a few hours and 22 days. Two patients recovered while the other two died. In the first fatal case which occurred in the 2-year-old child, co-amoxiclav was an additional suspected causative drug and severe liver involvement led to death. Another fatal case occurred in the 48-year-old patient who developed DRESS and subsequent hypersensitivity myocarditis.

Local situation and HSA's advisory

To date, HSA has not received any reports of DRESS associated with the use of azithromycin. The company has initiated a labelling update for the Zithromax® range of products to warn of reports of DRESS.

Healthcare professionals are encouraged to be vigilant to the signs and symptoms of DRESS in patients who are prescribed azithromycin. These may include rash, fever, lymphadenopathy, haematological abnormalities and multiorgan involvement. Early and prompt discontinuation of the offending drug is important to achieve the best outcome in patients with DRESS.

References

- 1 *Ann Intern Med* 2009; 150: 225-6
- 2 http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/carn-bcei_v24n2-eng.php#article2
- 3 *Br J Dermatol* 2013; 168: 391-401
- 4 *Am J Med* 2001; 110: 330-1
- 5 *Pediatr Dermatol* 2011; 28: 741-3

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■ Partnership in vigilance: Reporting adverse events related to health products ■

HSA encourages the reporting of all suspected adverse events to drugs and other medicinal substances (including herbal, traditional or alternative remedies). In particular, please report the following:

- 1 All serious adverse events which:
 - a) are life threatening or fatal
 - b) require inpatient hospitalisation or prolong existing hospitalisation
 - c) cause persistent or significant disability or incapacity
 - d) lead to congenital anomalies
 - e) are medically significant
- 2 All adverse events to recently marketed drugs that have been introduced into Singapore in the recent five years, regardless of their nature and severity

Please do not be deterred from reporting because some details are not known. Online reporting is available at www.hsa.gov.sg/ae_online. Forms can also be downloaded from the same website and submitted via the following methods:

- By mail to Vigilance and Compliance Branch (refer to full address on page 8)
- By fax to (65) 6478 9069
- By email to HSA_productsafety@hsa.gov.sg

Guide to better reporting of selected AEs



HSA has developed several guides for healthcare professionals to facilitate the reporting of selected AEs, namely anaphylaxis, cutaneous drug reactions and drug-induced liver injury (DILI). These guides provide information on the clinical presentation of the AEs and how to manage and report such AEs. They may

be downloaded via the hyperlink to "Guides on how to report for specific adverse events" at www.hsa.gov.sg/ae_online.

Safety surveillance of health products

Monitoring the safety of health products requires the support of healthcare professionals. It is by working in close partnership that safety signals related to health products can be promptly detected and measures taken to safeguard public health.

For more information on reporting of AEs, please go to www.hsa.gov.sg/ae_online.



Reference

- 1 <http://www.who-umc.org/graphics/28289.pdf>

Recent detection of adulterated products

'Powder packed in unlabelled pink sachet' and black pills labelled '特效风湿丸'

HSA recently issued a press release on 3 June 2015 to alert members of the public to two illegal products, namely 'powder packed in unlabelled pink sachet' and black pills labelled '特效风湿丸' ('special effect rheumatism pill'). The 'powder' was reported to HSA by a team of astute healthcare professionals from a local hospital. Subsequently, the willingness of the patient's relative in sharing crucial information on the source of the 'powder' aided in further investigations that led to the detection of the 'black pills'.

Adverse event reported

In April 2015, HSA received an adverse event (AE) report involving a Chinese female patient in her 40s who was admitted to hospital after presenting to the emergency department with altered mental state. She experienced auditory hallucinations, delirium, hyperglycaemia, electrolyte imbalances (hypokalaemia and hypophosphatemia) and possible iatrogenic Cushing's syndrome with moon facies. These symptoms were suspected to be associated with the consumption of 'powder packed in unlabelled pink sachet', which she had been taking for a number of years on an as-needed basis for pain relief. She also claimed that she had no recent intake of other medications or alcohol, and had no history of substance abuse.

Follow-up actions and investigations

The hospital team managed to convince the patient's relative to provide the source of the suspected product. Tests on the product found that it contained dexamethasone and chlorpheniramine.

Based on the information, HSA Enforcement officers conducted further investigations which led to the successful apprehension of



an illegal vendor, a local Chinese female peddler in her 60s. She would sell only to individuals whom she was familiar with and personally deliver the products to her customers.

During the course of HSA's investigation, another product, '特效风湿丸' ('special effect rheumatism pill') was uncovered at the home of the peddler. This was tested to contain chlorpheniramine, dexamethasone and bromhexine.

HSA's advisory

In view of the increasing trend of consumers turning to the use of alternative treatments such as herbal and traditional preparations, healthcare professionals are encouraged to ask their patients about the use of complementary health products when taking their medication history. This information may be useful for the differential diagnosis of AEs experienced by their patients. Healthcare professionals can also help to reinforce the message that patients should be wary of health products with exaggerated claims, from dubious sources, or which are not properly labelled with their ingredients.

General details to be included in an AE report are provided on page 4. HSA would like to highlight the importance of including additional details in the AE reports submitted that involve complementary health products (Table 1). For example, information on the source of a suspected illegal or adulterated product could aid in the apprehension of illegal peddlers and detection of other illegal products being sold.

We thank all AE reporters for being vigilant by contributing to the national AE reporting programme and doing their part for public safety.

Table 1. Additional information to include in AE reports involving complementary health products

Useful information	Rationale
Pictures of the product(s)	To determine the brand, manufacturer and labelled ingredients in each product To facilitate identification of the product when our officers conduct further assessment and investigation
Source of purchase <ul style="list-style-type: none"> Local or foreign address where product was purchased Online website address 	To allow for follow-up enforcement action Foreign address may be requested for information sharing with HSA's enforcement counterparts in other countries
Clinical test results (where relevant) <ul style="list-style-type: none"> Synacthen test and/or other relevant tests for suspected Cushing's Syndrome Liver panel results (from onset of injury till recovery and baseline results, if available) Blood/Urine toxicology results 	To assess possibility of exposure to exogenous steroids To assess the temporal relationship between the suspected product and liver injury To detect possible adulterants which the patient may be exposed to (e.g., hydroxyglibenclamide detected in a non-diabetic patient)
Other relevant information <ul style="list-style-type: none"> Concomitant medications used Pre-existing liver or biliary conditions History of alcohol consumption Serological markers of viral and autoimmune hepatitis 	To aid in the assessment of the adverse event by reviewing competing aetiologies

List of Dear Healthcare Professional Letters (DHCPL) issued by HSA, pharmaceutical and medical device companies between 2 April and 31 July 2015

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

Therapeutic products

- 9 Jun 2015 **Dobuject® (dobutamine) Injection 50mg/ml (Batch MA00X7F):**
Important advisory to visually inspect all ampoules prior to administration due to presence of precipitation found in Batch MA00X7F
- 30 Jun 2015 **Pomalyst® (pomalidomide):**
Updated product information on risk of serious hepatotoxicity (acute hepatitis), interstitial lung disease and cardiac failure
- 9 Jul 2015 **Jardiance® (empagliflozin):**
Risk of diabetic ketoacidosis (DKA) during treatment with sodium glucose co-transporter 2 (SGLT2) inhibitors
- 15 Jul 2015 **Invokana™ (canagliflozin):**
Risk of diabetic ketoacidosis (DKA) during treatment with sodium glucose co-transporter 2 (SGLT2) inhibitors
- 20 Jul 2015 **Forxiga® (dapagliflozin):**
Risk of diabetic ketoacidosis (DKA) during treatment with sodium glucose co-transporter 2 (SGLT2) inhibitors
- 23 Jul 2015 **Metoclopramide-containing products:**
Restrictions on the indications, dose and duration of use of metoclopramide-containing products in order to reduce the risk of neurological and other dose-related adverse reactions

Medical devices

- 15 Apr 2015 **Nellix EndoVascular Aneurysm Sealing System:**
Important update to the instruction for use (IFU) on key safety-related changes that are intended to mitigate the potential for EndoBag filling-related incidents
- 22 Apr 2015 **BIRMINGHAM HIP™ Modular Head (BMMH):**
Important update concerning patients implanted with BMMH, who may be at a greater risk for revision surgery due to a decline in the performance of the product
- 22 Apr 2015 **Zenith Alpha™ Thoracic Endovascular Graft:**
Important update to the instruction for use (IFU) following recent clinical findings of distal

- 23 Apr 2015 **Medtronic DBS System Extensions Models 37085 and 37086:**
Important update on the results from returned product analysis of Medtronic DBS system extensions with reports of high impedances. The letter reinforces device labelling specific to the handling of extensions and performing system integrity checks during implant procedures
- 25 May 2015 **Pulsar-18, Peripheral Self-expanding Nitinol Stent System:**
Voluntary recall of selected lots of stent length 200mm due to a higher than expected number of complaints regarding incomplete stent deployments with specific sizes and lots
- 3 Jun 2015 **Palindrome™ Precision SI Chronic Catheter, Palindrome™ SI Chronic Catheter, Palindrome™ Precision HSI Chronic Catheter, and Palindrome™ HSI Chronic Catheter:**
Voluntary recall of selected lots of Palindrome™ Chronic Catheter due to failure to meet the minimum silver release specification for the entire 30-day period
- 20 Jul 2015 **HeartWare® Ventricular Assist System (HVAS):**
Important information about potential issues which arose from HeartWare's review of complaints related to the HVAS and ongoing product performance monitoring
- 28 Jul 2015 **Birmingham Hip Resurfacing (BHR) system:**
Voluntary market removal of smaller size components of BHR system and contraindication of BHR system in females, due to observed revision rates which are higher than established benchmarks
- 29 Jul 2015 **Aesculap® Cementless Columbus Knee System:**
Important information on a higher than anticipated revision rate observed in the Australian market and the withdrawal of the device from the Australian market

Update to "Drugs approved in 2014"

The poster on "Drugs approved in 2014" that was distributed with the May 2015 issue of the HSA Adverse Drug Reaction News has been updated to add in drugs with new dosage forms. The updated poster can be downloaded via the hyperlink to "Poster of new products available in PDF" at www.hsa.gov.sg/adrbulletin.

NEW DOSAGE FORM	PHARMACOTHERAPEUTIC GROUP
Amlodipine 5 mg, 10 mg NORVASC® ODT (orodispersible tablet)	Antihypertensive agent (POM)
Amoxicillin (as amoxicillin trihydrate) 562.5 mg (IR layer), Amoxicillin (as amoxicillin sodium) 437.5 mg (SR layer), Potassium clavulanate : Microcrystalline cellulose 1 : 1 blend 62.5 mg (IR layer) AUGMENTIN SR™ tablet 1000/62.5 mg	Systemic antibacterial agent (POM)
Ibuprofen 200 mg, 400 mg NUROFEN® EXPRESS® liquid capsule	Systemic antiinflammatory & antirheumatic agent (P, POM)
Paracetamol 10 mg/ml PARACETAMOL-AFT® solution for infusion	Analgesic & antipyretic agent (POM)
Prednisone 1 mg, 2 mg, 5 mg Lodotra® modified-release tablet	Systemic corticosteroid preparation (POM)
Sildenafil 50 mg VIAGRA™ ODT (orodispersible) tablet	Agent used in erectile dysfunction (POM)
Sitagliptin, Metformin hydrochloride JANUMET® XR tablet 50 mg/500 mg, 50 mg/1000 mg, 100 mg/1000 mg	Oral antidiabetic agent (POM)

Risk of intussusception following rotavirus immunisation in Singapore

In recent years, post-licensure studies have detected a small risk of intussusception associated with the newer rotavirus vaccines, namely the monovalent (RV1) Rotarix® (GlaxoSmithKline Pte Ltd) and the pentavalent (RV5) RotaTeq™ (MSD Pharma (Singapore) Pte Ltd), in some populations. As the risk of intussusception could vary depending on geography, ethnicity, maternal and infant factors as well as environmental factors, a local study at KK Women's and Children's Hospital (KKH) was initiated to determine the risk of intussusception following rotavirus immunisation in Singapore.¹

Background

The safety concern of intussusception with rotavirus immunisation was first identified in 1999 with RotaShield®, which led to its withdrawal from the market.² The risk of intussusception was estimated at 10-20 cases per 100,000 Rotashield® recipients.³ Consequently, two newer oral rotavirus vaccines, RV1 and RV5, underwent large-scale clinical trials to ensure that there was no elevated risk with intussusception prior to their market approval in many countries (including US, Europe and Singapore) in the mid to late 2000s. However, recent post-licensure studies in some settings, namely Latin America (Mexico and Brazil), Australia and the US, have estimated the attributable risk of intussusception after rotavirus vaccination to be approximately 1.5 to 6 per 100,000 infants vaccinated.⁴⁻⁶

Local study on the risk of intussusception with RV1¹

A total of 86 infants hospitalised with intussusception at KKH prior to one year of age between 1 October 2005 and 30 September 2012 were identified. Of these, 20 infants had received either one (n=2) or two (n=18) doses of RV1. Four infants developed intussusception within three weeks of vaccination with RV1 dose 1 or 2. Using the self-controlled case series method, the authors found a significant increase in risk of intussusception in the 1- to 7-day risk period after RV1 dose 1, which did not change after adjusting for age (Relative incidence [RI] 8.36; 95% CI 2.42-28.96) (Table 1). No cases were reported during the 8- to 21-day risk period post dose 1. There was a smaller but non-significant elevated risk in the 1- to 7-day and 8- to 21-day risk period after RV1 dose 2. Although an eight-fold relative increase in risk may seem high, the actual excess risk associated with RV1 immunisation translates to about 1.5 cases per 100,000 infants immunised. This is the first study involving infants of Asian ancestry which demonstrated that the relative risk of intussusception post-RV1 immunisation is not higher in Asia despite differences in background intussusception incidence compared with United States, Latin America and Australia.

Rotavirus infection accounts for about a third of all acute gastroenteritis hospital admissions in children younger than five years

in Singapore.⁷ This study showed that a national rotavirus vaccination program with 90% coverage could potentially prevent 71% of all childhood hospitalisations due to rotavirus, with only a low risk of excess intussusception.

Local situation

Since the approval of RV1 in October 2005, more than 300,000 doses have been sold locally. To date, HSA has received 16 reports* of intussusception suspected to be associated with this vaccine, including the cases mentioned in the KKH study. Ten cases occurred within seven days of vaccination and one occurred on day eight of vaccination. Of these 11 cases, eight cases were reported with dose 1 and three cases with dose 2. The remaining five cases occurred beyond the 21-day risk period identified with rotavirus vaccination.⁶ There were also three reports of intussusception associated with RV5, which is less commonly used in Singapore. All the patients had either recovered or were recovering at the time of reporting.

* The data provided should not be used to draw comparisons on the safety of the different brands of rotavirus vaccines as this is confounded by factors such as extent of use and patient factors. The temporal association of these cases with rotavirus immunisation does not mean they were caused by the vaccine.

HSA's advisory

Healthcare professionals are advised to be vigilant to any symptoms indicative of intussusception (e.g., vomiting, palpable abdominal mass, abdominal pain or diarrhoea) following rotavirus vaccination. They are also advised to inform parents or caregivers to seek treatment early if the child experiences abdominal pain or bloating, often accompanied with persistent or bouts of crying, vomiting, blood in the stool or change in bowel movements at any time after each dose of the vaccine.

Healthcare professionals are encouraged to report any adverse events suspected to be associated with rotavirus vaccines to HSA as we continue to monitor these reports closely.

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Table 1. Age-adjusted RI of intussusception during risk periods by rotavirus vaccination dose

Dose (risk period)	No. of cases	Age (days)-adjusted RI (95% CI)	p value
Dose 1 (1-7 days)	2	8.36 (2.42-28.96)	0.001
Dose 2 (1-7 days)	1	3.09 (0.41-23.37)	0.28
Dose 2 (8-21 days)	1	1.54 (0.20-11.69)	0.67

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