ISSN: 0219 - 2152 December 2015 Vol.17 No.3

Adverse Drug Reaction News

Published by the Health Products Regulation Group, HSA and the HSA Product Vigilance Advisory Committee

Reflections on 2015 and Year End Greetings from the Editor-in-Chief

Editor-in-Chief (back row, third from left) and team

2015 marks the 17th year of the publication of the Adverse Drug Reaction (ADR) News bulletin and this December issue is the 51st issue published by the Vigilance and Compliance Branch, which also falls in the year Singapore celebrates its 50th birthday.

Over the years, the ADR News bulletin has established itself as a reputable regulatory newsletter that provides relevant and timely information on drug safety and adverse events associated with the use of health products to healthcare professionals. The healthcare professional boards have recognised it as a resource for continuing education, an achievement which we can be proud of.

As of 30 November 2015, we had highlighted 10 significant safety issues associated with the use of western drugs (including vaccines) and three cases of adulterated products through our ADR News bulletin. In consultation with HSA, companies issued 37 Dear Healthcare Professional Letters (DHCPLs) to convey important safety information and restrictions on the approved uses of the products, new safety risks observed in post-market, advice to minimise risk of adverse events and updates of safety information in product labels and Instructions For Use in medical devices.

Risk communication entails communicating risks not only to healthcare professionals but also to the public. Press releases are used to reach out to the public and warn them of adulterated and illegal products detected in the market. This is also to create awareness and educate our consumers so that they can make discerning choices on the purchase of health products. HSA has issued eight press releases as of end November this year on adulterated and illegal health products detected in Singapore. These included slimming, sexual enhancement, pain-relieving, health and wellness products, as well as cosmetics containing prohibited toxic substances.

Safeguarding public health underpins the work that we do in HSA. In this pursuit, we continue to look for innovative ways to carry out our public health mandate. Since 2008, we have embarked on several projects that utilise pharmacogenomics to enhance the safe use of drugs in Singapore. One significant achievement this year was that the HSA Pharmacogenetics Team was awarded the inaugural Mrs Tan Shook Fong-PSS Innovation and Scientific Research Award, in recognition of the scientific innovation and significant impact on pharmacy practice and pharmaceutical sciences in Singapore. The team detected an increased risk of serious skin reactions in our local population taking the anti-epileptic drug, carbamazepine and initiated clinical research studies in collaboration with SGH, NUH, CGH and NSC to investigate genetic associations behind serious drug-induced adverse reactions. This uncovered evidence of a strong association between the HLA-B*1502 gene and carbamazepine-induced serious skin reactions which led to testing for the HLA-B*1502 gene in all local patients of Asian ancestry starting on carbamazepine. This has been established as the standard of care in Singapore which is subsidised at restructured hospitals and institutions funded by the Ministry of Health.

All these achievements would not have been possible without the collaboration from our healthcare institutions and healthcare professionals. We look forward to more collaboration and working together with our healthcare professionals to safeguard public health.

On this note, together with the editorial team, we would like to wish all our readers a wonderful and joyful New Year!

Editor-in-chief
Chan Cheng Leng

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Possible Fanconi Syndrome associated with zoledronic acid

In August 2015, HSA received its first local ADR report of possible Fanconi Syndrome (FS) associated with zoledronic acid. The patient presented with multiple electrolyte imbalances, together with low uric acid levels and mild proteinuria approximately 10 days after receiving a single intravenous (IV) infusion of zoledronic acid 4mg for bone metastases secondary to prostate cancer. At the time of reporting, the outcome was unresolved, with the patient still requiring oral calcium replacement therapy.

Zoledronic acid (Zometa®, Novartis (Singapore) Pte Ltd) has been registered locally as a 4mg infusion since February 2005 for the treatment of osteolytic, osteoblastic, and mixed bone metastases of solid tumours and osteolytic lesions of multiple myeloma in conjunction with standard antineoplastic therapy, as well as for the treatment of hypercalcaemia of malignancy. There are also two other generic brands.

Another strength (5mg infusion) of zoledronic acid (Aclasta®, Novartis (Singapore) Pte Ltd) has been registered locally since March 2006 for the treatment of osteoporosis in post-menopausal women and in men at increased risk of fracture, prevention of glucocorticoid-induced bone mineral density loss, prevention of osteoporosis in post-menopausal women with increased risk of osteoporosis, and treatment of Paget's disease of the bone.

Local case report

The patient, a male in his fifties, had no past medical history of note and was not on long-term medication. He was admitted to hospital for right lower limb weakness and was subsequently diagnosed with prostate cancer with metastatic bone disease. A single dose of IV zoledronic acid 4mg was hence administered four days into admission. Other concomitant medications started during his hospital admission included gabapentin, tramadol, paracetamol/orphenadrine, ketoprofen, metoclopramide, lactulose, omeprazole, dexamethasone, bicalutamide, dopamine and several antibiotics.

Approximately 10 days later, the patient developed multiple acute electrolyte abnormalities including hypocalcaemia, hypophosphataemia, hypokalaemia and low uric acid levels. Paired urine sample analyses revealed high fractional excretion of uric acid and high urinary losses of phosphate, potassium and uric acid, indicating renal wasting of these electrolytes (Table 1). In addition, mild proteinuria (0.2g/L) was also detected. His other laboratory results were unremarkable. He did not have glucosuria.

FS was suspected to be induced by zoledronic acid based on the onset and clinical course of the patient. However, this patient did not present with all the classical and florid constellations of electrolyte abnormalities as expected with typical FS. Certain features that were lacking to support the diagnosis of FS included glucosuria and acidosis. In addition, the patient had severe vitamin D deficiency (<9ng/ml), which is a risk factor for hypocalcemia[1] and could have potentiated the persistent hypocalcaemia observed.

Literature reports

Several cases of zoledronic acid-induced FS have been reported in the literature.[2-4] The patients were administered zoledronic acid either for bone metastasis or malignancy-associated hypercalcaemia. The diagnosis of FS was established by the characteristic electrolyte abnormalities of blood and urine. In one of the cases, the diagnosis was further confirmed via renal biopsy, which showed scattered formation of cylinders inside the proximal renal tubules, infiltration of inflammatory cells around the proximal tubules and stroma of the same region, and interstitial oedema with lack of glomerular changes.[2] All three patients reported an improvement of renal tubular function after discontinuation of zoledronic acid treatment. Close monitoring of proximal tubular function during therapy with zoledronic acid was recommended by the authors of all the case reports.

Discussion

The diagnosis of drug-induced FS is usually suggested by a temporal relationship with exposure to a drug known to be toxic to the renal proximal tubule. However, it is worthwhile to note that with certain drugs such as tenofovir, toxicity can occur months or even years after establishing patients on treatment.[5]

This is the first report of zoledronic acid-induced FS reported locally. Healthcare professionals are advised to closely monitor the renal function of patients prescribed zoledronic acid so as to avoid the potential nephrotoxicity of the drug. Although some risk factors (i.e. elderly or very young population, pre-existing renal impairment and volume depletion) for drug-induced FS have been identified, in many cases it is unclear why patients develop toxicity while others do not. Pharmacogenomics has also been postulated to play a role in the development of drug-induced FS, although more research is required to establish this role.[5]

Healthcare professionals are encouraged to report any adverse drug reactions suspected to be associated with the use of IV zoledronic acid to the Vigilance and Compliance Branch of HSA.

HSA would like to take this opportunity to thank Dr Yeo Pei Shan, Senior Resident, Department of Endocrinology, Tan Tock Seng Hospital for her contribution to this article and partnering with us in our vigilance efforts to safeguard public health.

References

1 *Ann Oncol 2006; 17: 897-907*
2 *Endocr J 2012; 59: 1051-6*
3 *Intern Med 2011; 50: 1075-9*
4 *Gan To Kagaku Ryoho 2015; 42: 867-70*
5 *Q J Med 2014; 107: 261-9*
6 *Pediatr Nephrol 2015; 30: 1407-23*

About Fanconi Syndrome[5,6]

Fanconi Syndrome is a generalised dysfunction of the renal proximal tubules and can be inherited (i.e. Wilson's disease, Dent's disease) or acquired (i.e. drug-induced). The characteristic clinical features of Fanconi Syndrome include amino aciduria, organic aciduria, low molecular weight proteinuria, hypophosphataemia, normoglycemic glycosuria, metabolic acidosis, hypouricaemia, hypokalaemia and polyuria. However, some patients may only exhibit some of these features. These symptoms are a result of urinary wasting of solutes normally reabsorbed by the proximal tubule.

Drugs implicated in causing Fanconi Syndrome include ifosfamide, oxaliplatin, cisplatin, acetazolamide, tenofovir, valproic acid and antibiotics such as aminoglycosides and tetracyclines. Substantial recovery of proximal tubular function can occur after withdrawal of therapy but chronic damage may persist in some cases.

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Risk of pancreatitis associated with the use of deferasirox in paediatric patients

HSA would like to inform healthcare professionals of overseas cases of pancreatitis reported in paediatric patients following treatment with deferasirox.

Deferasirox (Exjade®, Novartis (Singapore) Pte Ltd) is an orally active iron chelator that has been registered in Singapore since 2008. It is approved for the treatment of chronic iron overload, either due to frequent blood transfusions (≥ 7ml/kg/month of packed red blood cells) in patients aged 6 years and older with beta thalassaemia major, or in patients aged 10 years and older with non-transfusion-dependent thalassaemia syndromes. Exjade® is also approved for the treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contraindicated or inadequate in patients with other anaemias, in patients aged 2 to 5 years, as well as in patients with beta thalassaemia major with iron overload due to infrequent blood transfusions.

About drug-induced pancreatitis[1,2]

Acute pancreatitis is usually characterised by abdominal pain and an increase in pancreatic enzymes in the blood and urine, with an overall mortality of approximately 5%. Epidemiological studies suggest that drug-induced pancreatitis is relatively rare, with an estimated incidence of 0.1% to 2%. Although most cases of possible drug-induced pancreatitis are mild, some have been reported to be severe or even fatal.

Drugs that have been reported to be associated with acute pancreatitis include azathioprine, tetracycline, valproic acid, isoniazid, metronidazole, oestrogens, angiotensin-converting enzyme (ACE) inhibitors and statins. The management of drug-induced pancreatitis includes the discontinuation of suspected drugs to prevent further progression of any ongoing pancreatic injury, intravenous fluid replacement, and close monitoring of blood pressure, cardiac and pulmonary status. In more severe cases, parenteral or enteral nutrition may be required if patients are unable to tolerate oral intake.

Overseas reports of acute pancreatitis with deferasirox

Recently, overseas adverse reaction reports received through the World Health Organisation (WHO) VigiBase®* suggest a signal of pancreatitis associated with the use of deferasirox in paediatric patients.[2]

As of March 2015, 14 reports of pancreatitis associated with the use of deferasirox in children and adolescents, aged between 4 to 16 years old, have been identified from VigiBase®. Deferasirox was the only suspected drug in 11 of these 14 cases. The remaining three cases also included other suspected drugs, such as azithromycin, ceftriaxone, hydroxycarbamide, amoxicillin, clarithromycin, omeprazole and deferoxamine. The time to onset was reported in nine cases and ranged from 17 days to over five years (median 11 months). This time interval is relatively consistent with the time to onset of drug-induced pancreatitis that had been reported in literature with various drugs including valproic acid, oestrogen, sulindac, statins and ACE inhibitors.[1] In addition, a positive dechallenge was also noted in six cases, which is supportive of a drug-induced effect.

** VigiBase® is a global database maintained and developed by the Uppsala Monitoring Centre (UMC) on behalf of the WHO. It consists of reports of adverse reactions received from national pharmacovigilance centres in more than 120 countries, including Singapore, and acts as a reference source for signal strengthening and ad hoc investigations.*

HSA's advisory

HSA has not received any local reports of pancreatitis associated with the use of deferasirox. The local package insert for Exjade® is currently in the process of being strengthened to include warnings on the risk of acute pancreatitis.

Healthcare professionals are advised to take into consideration the potential risk of acute pancreatitis in patients who are prescribed deferasirox, and to monitor for signs and symptoms which could be suggestive of pancreatitis, such as abdominal pain, nausea, vomiting or tenderness of the abdomen to touch, particularly in paediatric patients.

References

1 *Drug Safety 2008; 31: 823-37*
2 *Uppsala Monitoring Centre. SIGNAL newsletter, June 2015*

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■ **Possible Fanconi Syndrome associated with zoledronic acid** ■

Table 1. Relevant laboratory test results and subsequent change in therapy*

	Baseline (Day -20)	Day 1 (Onset of ADR)	Day 2	Day 3	Day 4	Day 5	Day 6	Day 29
Calcium, Adjusted (mmol/L)	2.54	**1.67** Started 6 cycles of IV calcium gluconate	**1.98** Started 2 cycles of IV calcium gluconate	**2.03** Started 2 cycles of IV calcium gluconate	**1.88** Started IV calcium gluconate and calcium carbonate tablets	2.32	2.32 Stopped IV calcium gluconate. Patient kept on calcium carbonate tablets	2.30 Continued calcium carbonate tablets
Phosphate (mmol/L)	1.2	**0.6**	**0.7**	**0.5**	0.9	0.8	0.9	1.1
Potassium (mmol/L)		4.0		3.5	**3.0** Started potassium citrate	3.9	4.2 Stopped potassium citrate	4.2
Magnesium (mmol/L)		0.8			**0.6** Started magnesium supplements	0.7	0.9	0.9
Sodium (mmol/L)		138		139	137	**133**		137
Bicarbonate (mmol/L)					26			
Vitamin D (ng/ml)				**<9** Started Cholecalciferol				
Parathyroid hormone (pmol/L)			7.1					

** Values in red are out of the normal reference range*

Adulteration of four 'S Lion Juice' products with tadalafil and analogues of PDE-5 inhibitors

Four products labelled as 'S Lion Juice' were tested by HSA and found to be adulterated with tadalafil and analogues of the phosphodiesterase-5 (PDE-5) inhibitors such as thiodimethylsildenafil, propoxyphenyl thioaidenafil and aminotadalafil (Table 1). The 'S Lion Juice' products were sold through the internet and marketed to contain natural ingredients including *Tribulus terresteris* and tea polyphenols for 'better health and brain power'. They were promoted to be suitable for consumers of all ages, including children and the elderly and carried claims such as to 'increase energy and stamina', 'improve sleep quality', 'improve brain functionality', 'strengthen bones, prevent osteoporosis', and 'help menopausal women regain their emotional health and strength'. A press release was issued by HSA on 14 August 2015 to alert members of the public to these adulterated products.

Table 1. Adulterants detected in 'S Lion Juice' products

Product	Adulterants detected
S Lion Juice 10 gm	Thiodimethylsildenafil and tadalafil
S Lion Juice 20 gm	Thiodimethylsildenafil
S Lion Juice Orange 10 gm	Propoxyphenyl thioaidenafil
S Lion Juice 1	Aminotadalafil and thiodimethylsildenafil

HSA's advisory

With the increasing trend of consumers turning to the Internet to purchase health products, healthcare professionals are encouraged to ask their patients about the use of such products. Patients often may not mention the use of such products as they are unaware that such products, especially those purchased online, may potentially be adulterated and could affect their health. For example, consumption of health products adulterated with PDE-5 inhibitors or their analogues could lead to adverse reactions such as visual disturbances, hypotension and cardiovascular effects such as tachycardia and palpitations.

Should a healthcare professional encounter a product which he suspects is adulterated, he could alert the Vigilance and Compliance Branch through filling up of an ADR report. An officer would contact the healthcare professional to gather more information so as to investigate the case and assess the causality. If the criteria for laboratory analysis are met, collection of the product for testing could be arranged.

In 2015, HSA had issued several press releases warning consumers of products that were found to be adulterated or to contain prohibited substances. A summary of these health products is provided in Table 2. More information on these products is available on the HSA website at *www.hsa.gov.sg*.

For more information on the reporting of suspected adulterated health products, please contact us at
Tel: *6866 3538* or
Email: *hsa_productsafety@hsa.gov.sg*.

Table 2. Prohibited substances detected in health products in 2015

Prohibited substances	Health products
Aminotadalafil and thiodimethylsildenafil	S Lion Juice 1
Chlorpheniramine and dexamethasone	Powder packed in unlabelled pink sachet
Chlorpheniramine, dexamethasone and bromhexine	Black pills labeled '特效风湿丸' ('special effect rheumatism pill')
Lignocaine	STUD 100® Male Genital Desensitizer Spray
Mercury	Pati IbuPutih by Janna Lawwa Day Creamy Face n Body White (Putih Gebu Kekal)
	Pati IbuPutih by Janna Lawwa Night Face n Body White (Putih Gebu Kekal)
Mercury and hydroquinone	Shantique Bellaza Facial Fuel Toner Mezzo
	Shantique Bellaza UV Pro Day Cream Mezzo
	Shantique Bellaza Rejuvenating Night Cream
Nortadalafil	Forta Plus for Men
Phenolphthalein	Skinny 22"
Propoxyphenyl thioaidenafil	S Lion Juice Orange 10 gm
Sibutramine and phenolphthalein	beFIT Total Garcinia Cambogia
Sildenafil	STARKRx Performance Enhancer
	Stark-Rx
	Maximum Strength Sexual Enhancer
Thiodimethylsildenafil	S Lion Juice 20 gm
Thiodimethylsildenafil and tadalafil	S Lion Juice 10 gm
Vinpocetine	BSN N.O.-Xplode 2.0 Advanced Strength
Yohimbine*	Nutrex Research Lipo 6 Black Ultra Concentrate
	Nutrex Research Lipo 6 Unlimited
	Primaforce Yohimbine HCL
Yohimbine* and deanol	Muscletech Neurocore Grape / Muscletech Fruit Punch
Yohimbine* and raubasine	Muscletech Hydroxycut Hardcore Elite
	Xenadrine XT Xtreme Thermogenic

** Although the products were labelled to contain yohimbine, it is a scheduled Poison and not allowed in nutritional supplements*

Collaboration with WHO-UMC: Advancing pharmacovigilance knowledge in the Asia-Pacific region

HSA, in collaboration with the World Health Organisation (WHO) and Uppsala Monitoring Centre (UMC), jointly organised the WHO-UMC-HSA Inter-Regional Pharmacovigilance (PV) Training Workshop held from 30 September to 2 October 2015 in Singapore. This is the third collaboration on PV training since the inaugural workshop held in 2010.

Singapore hosted over 50 participants including overseas delegates from ASEAN and the Asia-Pacific region (Brunei, Cambodia, Fiji, Hong Kong, Indonesia, Laos, Malaysia, Myanmar, Philippines, Tuvalu, Thailand and Vietnam). We were also privileged to have guest speakers from Japan, New Zealand, Pakistan, Sweden and Switzerland.

WHO-UMC's role in pharmacovigilance

WHO set up its Programme for International Drug Monitoring in 1961, and the Programme has been carried out by its collaborating centre in Sweden (UMC) since 1978. As part of UMC's mission to support and promote patient safety through effective and global PV practices, it provides consultation and training resources to medicines regulatory authorities worldwide. Training initiatives focus on imparting PV skills needed to set up and run a national PV programme as well as using PV tools developed by the UMC. These tools have been developed to support reporting, storing, structuring and generating analyses of individual case safety reports (ICSR) submitted by member countries for the purpose of facilitating PV work by regulatory authorities.

Partnership with HSA, Singapore

Singapore joined the WHO Drug Monitoring Programme in 1993 and has benefited from this programme through knowledge-sharing across its international network and utilising UMC's PV resources.

The aim of this collaboration was to conduct training workshops that would build and strengthen PV capabilities around the Asia-Pacific region while enhancing networking and working relationships among government regulators. The training programme across the three workshops held between 2010 and 2015 was developed to cover the basics of PV, such as risk detection, assessment and communication, as well as advanced topics on pharmacoepidemiology, data mining and pharmacogenomics. The programme was well-received and participants provided feedback that the training curriculum was comprehensive and applicable to their daily work.

2015 Pharmacovigilance Training Workshop

This year, the training sessions were conducted by distinguished local and international experts. The trainers comprised the following:

- *Dr Ruth Savage*, Medical Assessor and Senior Research Fellow, New Zealand Pharmacovigilance Centre
- *Ms Paula Alvarado*, Head of Global Communications, UMC
- *Ms Anna Hegerius*, Senior Specialist, Education and Training, UMC
- *Ms Helena Wilmar*, Senior Specialist, Pharmacovigilance Consulting, UMC
- *Dr Daisuke Tanaka*, Technical Officer, Safety and Vigilance Medicines Group, WHO
- *Dr Syed Khalid Bukhari*, Country Advisor, Medicine and Health Products, WHO
- *Dr Yusuke Matsunaga*, Reviewer, Office of Safety II, Pharmaceuticals and Medical Devices Agency (PMDA), Japan
- *A/Prof Thoon Koh Cheng*, Head and Senior Consultant, Infectious Disease Service, KK Women's and Children's Hospital
- *Dr Dorothy Toh*, Acting Assistant Group Director, Vigilance, Compliance and Enforcement Division, HSA

The participants were given an overview of the PV systems in different countries, namely Japan and Singapore, Pakistan's experience with substandard and counterfeit medicines, the spectrum of PV methods and the different strategies to promote an ADR reporting culture. This was followed by the basics on safety signal detection, causality assessments and effective risk communications.

Conclusion

The training workshop was successfully conducted. PV entails application of science and utilisation of technology. It is therefore crucial that regulators continue to keep abreast with this dynamic discipline through training and education. It is hoped that participants armed with the new-found knowledge on PV will apply these concepts and achieve their public mandate of protecting national health and safety.

Feedback sought on the ADR News bulletin going fully electronic

As the ADR News bulletin approaches its 18th year of publication, it is timely to once again seek some feedback from our readers on your preferred mode of dissemination of the bulletin.

In 2011, healthcare professionals were surveyed to evaluate the overall performance (effectiveness) of HSA's risk communications tools and channels, focusing on promptness and timeliness of the dissemination of information, as well as the adequacy of the communications channels used (i.e. electronic or hard copies). 82% of the respondents indicated that the ADR News bulletin was relevant to their practice, with 73% of the respondents indicating the information in the ADR News bulletin is timely most of the time. A summary of key findings from the survey is provided below.

Most of the healthcare professionals rated the ADR News bulletin very highly in terms of the quality of information provided (91%), and its design and layout (67%). When queried if the Continuing Medical/Professional Education point (CME/CPE) accredited through reading the publication was the motivation for healthcare professionals to read the bulletin, 61% responded that it was not the case. Healthcare professionals responding to the 2011 survey also did not show a strong preference to whether the ADR News bulletin should be made available to them in hard copy or electronic copy or both.

Consideration for going paperless – We want your feedback!

While the feedback from the 2011 survey was generally positive, it has been four years since this feedback was obtained and perceptions may have changed with new technological advancements and the evolving healthcare landscape.

The hard copy of the ADR News bulletin is currently delivered by post to all healthcare professionals registered in Singapore. In addition, current and past issues of the bulletin are also available online at *www.hsa.gov.sg/adrbulletin*. As part of global efforts to reduce our carbon footprint and to go green, the editorial team is considering disseminating only electronic copies of the ADR News bulletin moving forward. We would like to seek your feedback on the following:

Would you prefer to receive only an electronic version of the HSA ADR News bulletin? Yes/No

Comments, if any:

Please email your response to *HSA_Productsafety@hsa.gov.sg* with the email title: Electronic.

Your feedback is invaluable to us and we look forward to your continued support in making the ADR News bulletin a relevant and informative read.

Summary of key findings from the 2011 Risk Communication survey

HSA communicates safety information to healthcare professionals using a variety of tools and channels, including the following:

1. Electronic dissemination of information including Dear Healthcare Professional Letters (DHCPL) via emails (MOH Alert[a] and HSA Product Safety mailbox[b])
2. HSA Website (containing Product Safety Alerts, summary of DHCPL, Product Recalls, Safety-related label amendments, Press Releases, HSA Updates)
3. HSA Adverse Drug Reaction (ADR) News bulletin[c]

[a] MOH Alert harnesses IT connectivity to disseminate urgent DHCPLs to more than 15,000 doctors, dentists and pharmacists registered with their professional councils

[b] Emails sent from the HSA Product Safety mailbox are disseminated to the senior management and heads of medical departments of the public and private healthcare establishments, with a request for them to disseminate the email internally to the relevant healthcare professionals

[c] A 4-monthly bulletin containing recent safety drug issues that is disseminated by post to all registered doctors, dentists and pharmacists. A softcopy is also available on the HSA website

A total of 736 responses were received for the 2011 Risk Communication survey, representing 5.75% of the survey recipients. Of these, only 92 (12.5%) respondents chose to respond online.

a) Sources of information on important health product issues

When the respondents were asked on how they usually obtain their important health product safety issue information, two main sources were cited: emails via MOH Alert (75%) and hard copies of the HSA ADR News bulletin (79%) (Figure 1). Other frequently used sources used included media and emails via HSA Product Safety mailbox.

b) Preferred mode of obtaining health product safety information

A similar pattern was seen when respondents were asked about their preferred mode of obtaining such information.

Figure 1. Sources of information on important health product safety issues

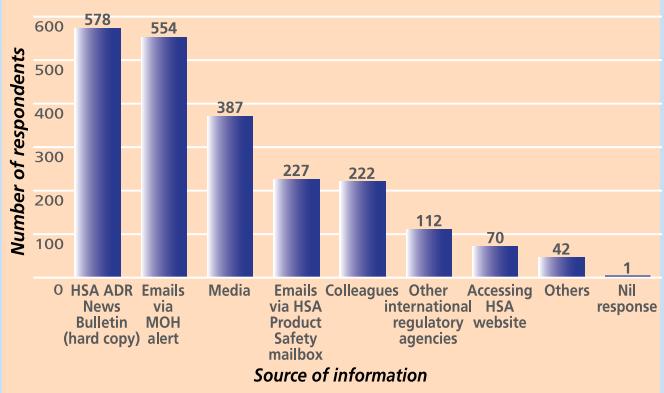
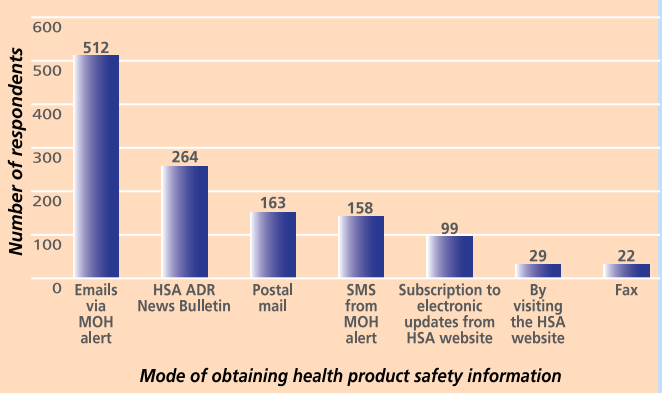


Figure 2. Preferred mode of obtaining health product safety information



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List of Dear Healthcare Professional Letters (DHCPL) issued by HSA, pharmaceutical and medical device companies between 1 August and 30 November 2015

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

Therapeutic products

14 Aug 2015 **Prolia® (denosumab 60mg) and Xgeva® (denosumab 120mg):**
Important advisory to monitor for the development of hypercalcaemia following discontinuation of treatment in paediatric patients

17 Aug 2015 **Atarax™ (hydroxyzine):**
New restrictions for hydroxyzine-containing medicines to further minimise the known risk of QT prolongation, particularly in the most vulnerable groups. Hydroxyzine should also be used at the lowest effective dose, for the shortest possible treatment duration

7 Oct 2015 **Lescol® capsule 40mg (fluvastatin):**
Reduction in shelf-life from 36 months to 24 months due to the stability profile of fluvastatin sodium. Novartis Singapore also plans to discontinue Lescol® capsule 40mg by December 2015

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■ Summary of key findings from the 2011 Risk Communication survey ■

70% indicated their preference for emails via the MOH Alert channel, while 36% preferred obtaining information using the HSA ADR News bulletin (Figure 2).

c) Relevance and timeliness of communications

Healthcare professionals were mostly satisfied with the relevance and timeliness of the dissemination of the safety information. Most (75%) of the respondents felt that the speed and timeliness at which HSA provides them with urgent and important health product safety information is either excellent or good.

It is also heartening to know that healthcare professionals regard the ADR News bulletin as a quality source of health product safety information, providing relevant and timely information to them.

d) New media platforms

The survey also attempted to explore the attitudes of healthcare professionals towards the use of new media platforms such as Twitter and Facebook in disseminating health product safety information. The majority (79%) of the respondents were not supportive of the use of new media platforms, with several of the respondents providing strong views against their use in disseminating health product safety information.

Acknowledgements
The editorial team would like to thank Ms Lim Ping Siew for her invaluable contributions to the 2011 Risk Communication survey and the healthcare professionals who have submitted the survey responses.

30 Oct 2015 **Zantac® tablet 150mg (ranitidine):**
Possibility of brown discoloration present in some tablets due to impurities arising from the degradation of ranitidine, which occur in the presence of moisture

Medical devices

18 Aug 2015 **Activa® PC, Activa® SC, Activa® RC, Kinetra® and Soletra® Devices used in Deep Brain Stimulation (DBS) Therapy:**
Updated product information to include additional warnings and adverse events that is intended to assist in patient management

9 Sep 2015 **rHead, uHead, Sigmoid Notch, ReMotion and Radio Capitellum:**
Voluntary recall of selected lots due to a potential breach in sterile packaging during transportation

11 Sep 2015 **LFIT V40 Tapers Vitallium Femoral Heads:**
Voluntary recall of selected lots due to the potential failure of the assembly of the affected femoral heads with their corresponding V40 stem trunnion at the time of surgery

16 Sep 2015 **Medtronic 23mm Engager™ Transcatheter Aortic Bioprosthesis:**
Voluntary recall following a review of the 2-year follow-up data of Engager European Pivotal Trial, which has shown that 16 of 32 subjects implanted with a 23mm device had a mean gradient of ≥ 20mmHg at some point after the implant (average mean gradient at 2-year follow up: 22.0 ± 7.5mmHg). A mean gradient of 20-40mmHg is associated with mild stenosis as per the Valve Academic Research Consortium (VARC) -2 guideline

6 Oct 2015 **Thoratec® HeartMate II® LVAS Pocket System Controller:**
Important advisory to monitor the expiration date of the 11V Lithium-Ion Backup Battery due to a recent trend in reports of serious injuries and deaths associated with patients attempting to exchange System Controllers in response to Advisory alarms triggered when the backup battery is not replaced by the first day of the month of the battery's expiration date

12 Oct 2015 **Silimed products in Singapore:**
Suspension of supply of all medical devices manufactured by Silimed Industria De Implantes Ltda in Singapore due to the suspension of European approval (CE certificate) for devices and the ISO quality management system certificates for the manufacturing facility. This followed a recent inspection of their manufacturing plant in Brazil which discovered the presence of particles on the surface of some breast implants

19 Nov 2015 **InSync® III Cardiac Resynchronization Therapy Pacemakers (CRT-P) Models 8042, 8042B, 8042U:**
Advisory for affected models as pacing function of the implants may be impacted due to the battery's inability to supply sufficient electrical current

Drug-drug interaction between repaglinide and clopidogrel: Potential risk of hypoglycaemia

HSA would like to highlight the findings of a recent study which concluded that co-administration of repaglinide and clopidogrel results in an increased systemic exposure to repaglinide, due to strong inhibition of CYP2C8 by clopidogrel acyl-β-D-glucuronide. This could in turn enhance the glucose-lowering effect of repaglinide, thereby predisposing patients to the risk of hypoglycaemia.

Repaglinide (Novonorm®, Novo Nordisk Pharma (Singapore) Pte Ltd) is an oral antidiabetic agent that has been registered locally since January 1999 for the treatment of adults with type 2 diabetes mellitus. It is approved for use as monotherapy in patients whose hyperglycaemia is inadequately controlled by lifestyle modifications or in combination with metformin in patients whose hyperglycaemia is inadequately controlled by metformin alone.

Clopidogrel (Plavix®, Sanofi-Aventis Singapore Pte Ltd) is an antiplatelet agent that has been registered locally since June 1998. It is approved for the prevention of atherothrombotic events in adults with recent myocardial infarct, recent stroke, established peripheral arterial disease or acute coronary syndrome, as well as in combination with aspirin for the prevention of atherothrombotic and thromboembolic events in selected adult patients with atrial fibrillation. Currently, there are 12 generic clopidogrel-containing products registered in Singapore.

Study findings[1]

In a study conducted by Tornio *et al*, nine healthy subjects received clopidogrel (300mg on day 1, followed by 75mg daily for 2 consecutive days) or a single dose of placebo in a crossover manner. Repaglinide was co-administered as single dose of 0.25mg on days 1 and 3 of clopidogrel treatment and on the day of placebo administration. Co-administration of repaglinide and clopidogrel was shown to result in an increase in repaglinide systemic exposure ($AUC_{0-\infty}$) by 5.1-fold and 3.9-fold on days 1 and 3 of clopidogrel treatment, respectively, when compared with placebo ($p<0.001$). The elimination half-life of repaglinide was also observed to be prolonged by 42% and 22%, respectively ($p<0.005$). The blood glucose levels of study subjects were significantly lower in both clopidogrel phases as compared to placebo, reaching a minimum concentration of 3.3 ± 0.6mmol/L, 3.9 ± 0.6mmol/L and 4.4 ± 0.5mmol/L following administration of repaglinide 1 hour after dosing with clopidogrel 300mg (day 1), clopidogrel 75mg (day 3) or placebo, respectively.

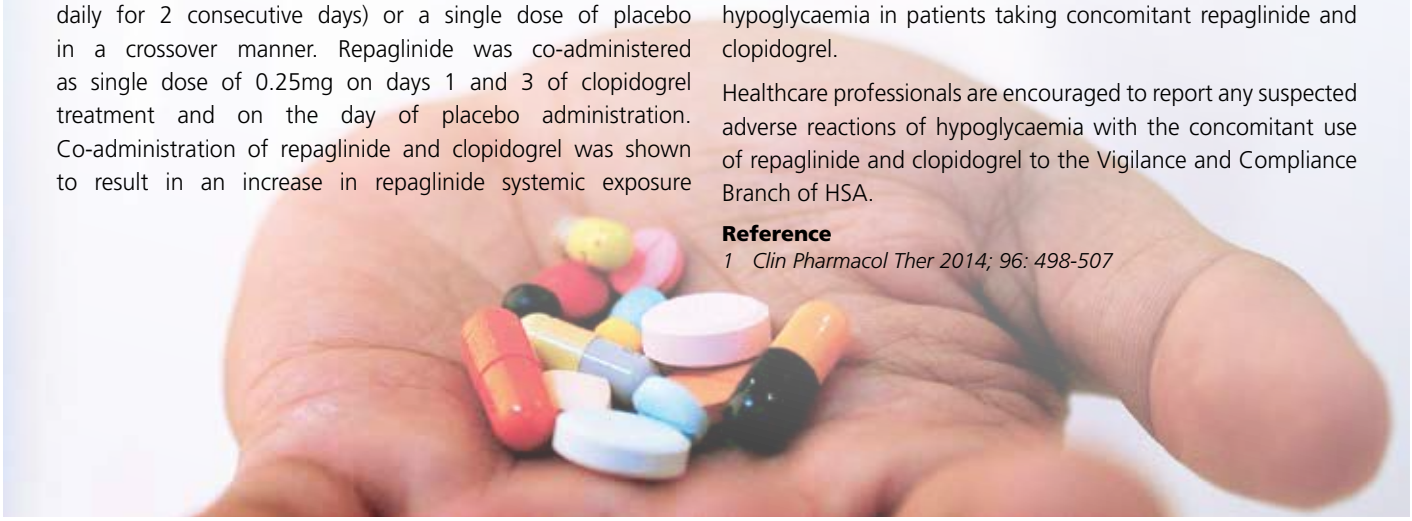
This study also identified clopidogrel acyl-β-D-glucuronide, the metabolite of clopidogrel, as a potent time-dependent inhibitor of CYP2C8 *in vitro*. In view of the study findings, the study authors recommended that concomitant use of repaglinide and clopidogrel is best avoided. They also postulated that clopidogrel is likely to cause drug-drug interactions with other CYP2C8 substrates, such as montelukast, paclitaxel and pioglitazone, which warrant further clinical studies.

HSA's advisory

To date, HSA has not received any reports of hypoglycaemia associated with the concomitant use of repaglinide and clopidogrel. HSA is working with the companies to strengthen the local package inserts of both products to include warnings and precautions with regard to the potential risk of hypoglycaemia arising from their drug-drug interaction.

Healthcare professionals are advised to consider the above safety information when prescribing repaglinide and clopidogrel together, and to monitor for signs and symptoms of hypoglycaemia in patients taking concomitant repaglinide and clopidogrel.

Healthcare professionals are encouraged to report any suspected adverse reactions of hypoglycaemia with the concomitant use of repaglinide and clopidogrel to the Vigilance and Compliance Branch of HSA.



Reference

1 *Clin Pharmacol Ther 2014; 96: 498-507*

Please send your enquiries, comments and suggestions to:

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