

Azithromycin and potential risk of QT prolongation

Two recent research studies have strengthened the evidence regarding the potential risk of QT prolongation associated with the use of azithromycin. In the light of this latest data, healthcare professionals are advised to be aware of the risk of Torsades de Pointes and fatal arrhythmia when considering azithromycin as a treatment option for patients who are at risk for cardiovascular events. These patient groups include¹:

- Patients with known prolongation of the QT interval, a history of Torsades de Pointes, congenital long QT syndrome, bradyarrhythmias, or uncompensated heart failure
- Patients on drugs known to prolong the QT interval
- Patients with ongoing proarrhythmic conditions such as uncorrected hypokalaemia or hypomagnesaemia, clinically significant bradycardia, and patients receiving Class IA (quinidine, procainamide) or Class III (amiodarone, sotalol) antiarrhythmic agents.
- Elderly patients and patients with cardiac disease who may be more susceptible to the effects of arrhythmogenic drugs on the QT interval

Background

Azithromycin is an azalide, a subclass of macrolide antibiotics derived from erythromycin that is widely used both orally and intravenously for the treatment of upper and lower respiratory tract infections and other infections involving susceptible organisms. There are currently 17 registered azithromycin-containing products in Singapore, including the ZithromaxTM range of products (Pfizer Pte Ltd), ZmaxTM (Pfizer Pte Ltd) and 11 other generic products.

Although closely related macrolide drugs such as erythromycin and clarithromycin are known to increase the risk of serious ventricular arrhythmias and are associated with an increased risk of sudden cardiac death, azithromycin has previously been reported to be better tolerated than other macrolides, and has minimal side effects.² However, within the last year, two research studies have provided evidence on the risk of QT prolongation associated with azithromycin.

Publication in New England Journal of Medicine (NEJM)³

One of the studies published in the NEJM in May 2012 suggested a higher risk of cardiovascular deaths and deaths from any cause in persons treated with a 5-day course of azithromycin compared to persons treated with amoxicillin, ciprofloxacin, or no drug. There were some limitations to this study, such as potential bias due lack of randomisation to the antibacterial drugs, outpatient setting investigation where it is likely that few patients were treated for severe or life-threatening infections, and the method of determination of cardiovascular deaths through death certificates instead of full medical records. Despite these, the study was noted to be methodologically sound and supportive of the validity of the overall findings.

The estimated excess risk of cardiovascular death compared with amoxicillin varied considerably with the patients' baseline cardiovascular risk, from roughly 1 in 111,000 among healthier patients to 1 in 4,100 among high-risk patients. The duration of the elevated risk of all-cause mortality and of cardiovascular death corresponded to the duration of azithromycin therapy. The increase in total deaths was determined to be attributed to cardiovascular deaths

and not from other causes. The excess risk of cardiovascular death, especially of sudden death, was consistent with arrhythmias from drug-related QT prolongation.

Clinical QT study conducted by manufacturer¹

The manufacturer of azithromycin also conducted a randomised, placebo-controlled parallel trial to assess the effects of azithromycin on the QT interval in 116 healthy adults. These subjects received either chloroquine (1000mg) alone or in combination with azithromycin (500mg, 1000mg, and 1500mg once daily). Co-administration of azithromycin increased the QTc* interval in a dose- and concentration-dependent manner. In comparison to chloroquine alone, the maximum mean (95% upper confidence bound) increases in QTcF** were 5ms (10), 7ms (12) and 9ms (14) with the co-administration of 500mg, 1000mg and 1500mg azithromycin, respectively.

* As the QT interval has an inverse relationship to heart rate, the measured QT interval is routinely corrected by means of various formulae to a value known as the QTc interval which is less dependent on the heart rate

** the maximum mean difference in QT duration corrected for heart rate by the Fridericia's Formula

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Intramuscular medroxyprogesterone and injection site necrosis and atrophy

HSA would like to inform healthcare professionals about overseas reports of injection site necrosis and atrophy associated with the use of intramuscular medroxyprogesterone.

Medroxyprogesterone acetate (Depo-Provera®, Pfizer Pte Ltd) is a synthetic progestin that is structurally related to the endogenous hormone progesterone. In Singapore, it is available as an intramuscular injection for use in contraception, treatment of endometriosis and menopausal vasomotor symptoms, adjunctive and/or palliative treatment of recurrent and/or metastatic endometrial or renal carcinoma as well as the treatment of hormonally-dependent, recurrent breast cancer in postmenopausal women.

Postmarketing reports of injection site necrosis and atrophy

As of 31 July 2012, a total of 103 medically confirmed global cases of injection site reactions associated with the intramuscular route of administration of medroxyprogesterone were reported to the company. Of these reports, 31 (30.1%) were serious. These injection site reactions described events such as injection site atrophy, atrophy, skin atrophy, lipoatrophy, injection site necrosis, necrosis, fat necrosis, injection site ulcer, and muscle necrosis.



In 46 cases (44.7%), there was insufficient information to allow a meaningful medical assessment. Missing information included site of reaction, site of administration, dates of therapy, dates of event onset, and/or the dose administered. There were 21 (20.4%) cases where intramuscular medroxyprogesterone injection was reported to be administered at the thigh region instead of the recommended deltoid or gluteal region. There were 10 (9.7%) cases where errors in the administration of intramuscular medroxyprogesterone were involved. For the remaining 26 cases (25.2%), the role of intramuscular medroxyprogesterone in the development of injection site atrophy,

necrosis, lipoatrophy, skin atrophy, skin necrosis and injection site ulcer could not be ruled out.

HSA's advisory

HSA has not received any reports on injection site reactions associated with the use of intramuscular medroxyprogesterone. HSA is working with the company to further strengthen the warnings in the local package insert for Depo-Provera® to include injection site necrosis and skin atrophy as potential injection site reactions.

Healthcare professionals are reminded to take into consideration the above safety updates when prescribing intramuscular medroxyprogesterone and are encouraged to report any suspected reactions to the Vigilance Branch of HSA.

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Actions taken by US Food and Drug Administration (FDA)⁴

The US FDA has updated the azithromycin US package inserts to strengthen the Warnings and Precautions section with information related to the risk of QT interval prolongation and Torsades de Pointes. Information regarding the results of the clinical QT study which showed that azithromycin can prolong the QTc interval has also been added.

Local Situation

From 1996 to-date, HSA has received 181 ADR reports associated with the use of azithromycin. Of these reports, there was one case of QT prolongation in a 75-year-old patient with positive rechallenge. There was also one reported case of palpitations in a 38-year-old patient.

HSA's action and advisory

HSA is currently working with the relevant product licence holders to update the package inserts of all azithromycin products to strengthen the warnings regarding the risk of abnormal cardiac rhythms.

Apart from azithromycin, other macrolides such as erythromycin and clarithromycin or non-macrolides such as the fluoroquinolones, are known to have the potential for QT prolongation or other significant side effects. Healthcare professionals are advised to take into consideration these factors when prescribing antibacterial treatment for their patients. Healthcare professionals are also encouraged to report all suspected adverse reactions associated with azithromycin to the Vigilance Branch of HSA.

References

- 1 Zithromax® US package insert. Revised January 2013
- 2 http://www.actabiomedica.it/data/2006/1_2006/1russo.pdf
- 3 N Engl J Med 2012; 366: 1881-90
- 4 <http://www.fda.gov/drugs/drugsafety/ucm341822.htm>

AE case in focus: Test yourself



A 60-year-old Chinese female presented with fever, cough and complaints of lethargy for the past two to three weeks. Upon hospitalisation, her condition rapidly deteriorated into Type 1 respiratory failure and she was transferred to the

Medical Intensive Care Unit for ventilation. CT Thorax showed extensive ground glass consolidation with patchy dense consolidation and air bronchogram. Her culture results were negative.

She has a past history of recurrent urinary tract infection (UTI) with Grade 1 vesico-ureteric reflux and was on long-term nitrofurantoin for the last 6 months for prophylaxis of recurrent UTI based on culture sensitivity. Her concomitant medications include calcium carbonate, vitamin B complex, rivastigmine and alendronic acid.

- Could the acute respiratory problem be drug-induced?*
- If so, what is the most likely suspected drug?*
- If you are uncertain that this is a drug-induced reaction, would you still report this as a suspected AE to HSA?*

This case study is based on an actual AE report submitted to HSA but with minor changes to protect patient confidentiality. We would like to take this opportunity to thank Dr Chew Si Yuan for his contribution to drug safety education.

Answers to the case study can be found on page 7.

New enhancements to the medical device regulatory framework

On 1 January 2013, HSA introduced two new enhancements to the medical device regulatory framework to facilitate faster access and lower regulatory fees for these products.

The first initiative is the expedited registration routes for Class C and D medical devices, following the earlier approach adopted for the lower risk Class B medical devices. However, in view that Class C and D comprise higher risk devices (e.g., CT-scanners, haemodialysers, breast implants), the expedited registration routes have been tailored to ensure that patient safety is not compromised. As with Class B devices, this has been achieved through judicious referencing of HSA's medical device independent reference regulatory agencies and safe history of use of these products. In addition, medical devices with significant impact on public health (e.g., implantable pacemakers, cardiovascular stents, HIV test kits) would be excluded from this route.

The second initiative is the introduction of a set of Quality Management System (QMS) requirements derived from the Good Distribution Practice for Medical Device in Singapore (GDPMDS). These QMS requirements are applicable to importers and wholesalers who solely deal with low risk Class A medical devices and will no longer require a third party independent audit, which is required of importers and wholesalers of higher risk medical devices. Highlights of the enhancements are outlined in Table 1.

HSA would like to take this opportunity to highlight that even though a medical device may be registered under the Health Products Act, the supply and use of any medical device in Singapore should also comply with the requirements under other applicable legislations (e.g., Private Hospitals and Medical Clinics Act, Professional Acts, Radiation Protection Act). Professional Acts include the Medical Registration Act, Dental Registration Act and others.

HSA views healthcare professionals as important partners in the successful implementation of the medical device regulatory framework. We look forward to our continued partnership in ensuring that safe, effective and quality medical devices are introduced and used in Singapore. Feedback or enquiries on the enhancement to the regulatory framework can be made through email to HSA_MD_Info@hsa.gov.sg.

Table 1. Overview of new enhancements effective from 1 January 2013
(Details are available on the HSA website at www.hsa.gov.sg)

Enhancements	Potential benefit(s) to HSA's stakeholders
<p>Expedited Registration Route for Class C and D medical devices</p> <ul style="list-style-type: none"> ■ Devices qualifying for this route are <ol style="list-style-type: none"> i. Class C devices which have already been approved by at least one independent regulatory agency¹ and marketed in that jurisdiction or in Singapore without any safety concerns for at least three years; or ii. Class C and D devices which have already been approved by two independent regulatory reference agencies¹. ■ Medical devices excluded from the expedited registration routes <ul style="list-style-type: none"> ● Active Implantable Medical Devices (e.g., pacemakers, neurostimulators) ● Implantable devices in direct contact with the central circulatory system or central nervous system ● Hip, knee and shoulder joint replacement implants ● Devices incorporating a registrable drug in an ancillary role ● IVD devices intended for: <ul style="list-style-type: none"> ▲ HIV testing (screening and diagnosis) ▲ Blood/tissue donor compatibility testing ■ Regulatory evaluation fees for expedited Class C and expedited Class D routes are reduced by \$500 and \$300 per application to \$3,000 and \$5,400, respectively (with reference to abridged evaluation fees). ■ Turnaround time for the expedited Class C and expedited Class D routes is reduced from 160 to 120 working days and 220 to 180 working days, respectively (with reference to turnaround time for abridged evaluation). 	<p>The enhancements will result in faster access for Class C and D medical devices. Applicants will also benefit from lower regulatory fees and shorter turnaround time for registration.</p>
<p>Quality Management System for Class A medical device dealers</p> <p>The assessment of this group of dealers (importers and wholesalers) will be carried out by HSA and no third party certification is required.</p>	<p>Class A medical device dealers will benefit from cost reduction since no third party certification is required.</p>

¹ US Food and Drug Administration (FDA), EU Notified Bodies, Australian Therapeutic Goods Administration (TGA), Health Canada and Japan Ministry of Health, Labour and Welfare



Analysis of adverse event reports for Year 2012

Singapore has retained the top ranking in terms of the number of valid reports per million inhabitants that was submitted to the World Health Organisation (WHO) global database. This is according to the October 2012 report published by WHO's Uppsala Monitoring Centre (Figure 1).

In 2012, the adverse event (AE) monitoring programme administered by the Vigilance Branch of HSA captured a total of 22,506 valid local AE reports suspected to be related to health products. Reports lacking important details such as names of suspected drugs and AE descriptions are regarded as invalid reports and are not captured into the national AE database as they cannot be assessed for causality.

On the average, about 1,900 reports were received per month. At the end of 2012, there were approximately 133,300 AE reports captured in the national database since data collection started in 1993.

The majority of the AEs reported were associated with pharmaceuticals/biologics (98%) followed by vaccines (1.3%). Complementary health products including Chinese Proprietary Medicines, health supplements and other traditional medicines accounted for 0.7% of the reports.

Figure 2 provides a breakdown of the number of valid reports captured in the AE database from 2002 to 2012 based on the date of receipt of the reports. HSA started receiving electronic reports transmitted from the public healthcare institutions via the Critical Medication Information Store (CMIS) in January 2006. This accounts for the significant increase in report numbers observed in 2006.

Descriptive Analysis of AE reports

Patient Demographics Profile

More AEs were reported to occur in females (58%) than in males (40%), with a lack of information for 2% of the cases. Patients between 50 to 69 years of age accounted for the largest proportion (30%) of the reports.

Reporter type and source

Majority of the AE reports came from polyclinics (51%) and public hospitals (46%), with 2% from drug companies and 1% from private clinics/hospitals.

Healthcare professionals, namely doctors (88.9%) and pharmacists (7.2%), contributed substantially to the reports. Three AE reports were received from Traditional Chinese Medicine Physicians.

AEs by System Organ Class

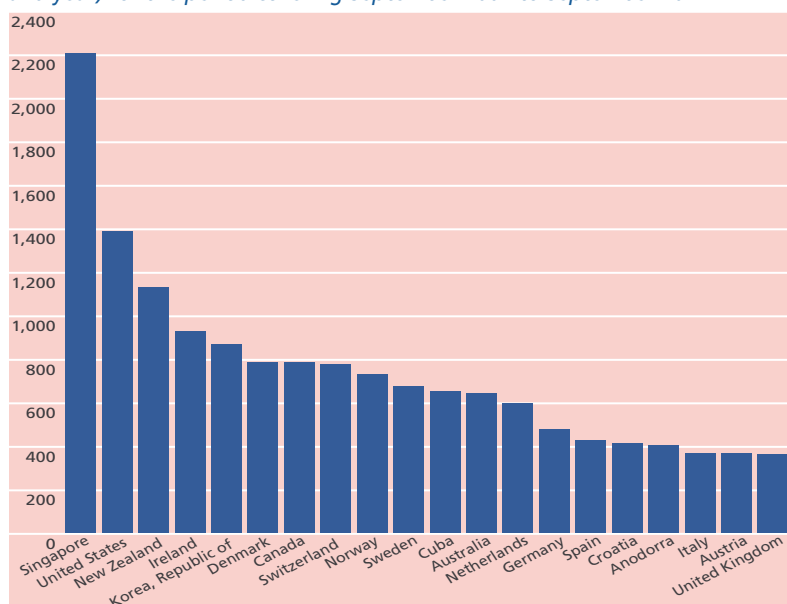
Most of the reports were skin-related disorders (50.9%), followed by those affecting the body as a whole (i.e. general disorders such as pain, fever, oedema) (18.0%), and respiratory disorders (6.9%). Table 1 provides the full listing of top 10 AEs based on system organ class.

Drugs suspected of causing serious blood, hepatic and skin reactions are listed in Table 2.

Analysis of vaccine adverse event (VAE) reports

In 2012, a total of 290 VAE reports were received. Majority of the reports (80%) involved children less than 12 years of age, which corresponds with the age group of vaccinees

Figure 1. Active ICSRs* in the WHO global ICSR database (per million inhabitants and year) for the period covering September 2007 to September 2012



* Individual Case Safety Reports

[Ref: Uppsala Monitoring Centre, Uppsala Reports 59, October 2012, page 7]

Figure 2. Number of valid reports captured in the AE database from Year 2002 to 2012 based on date of receipt

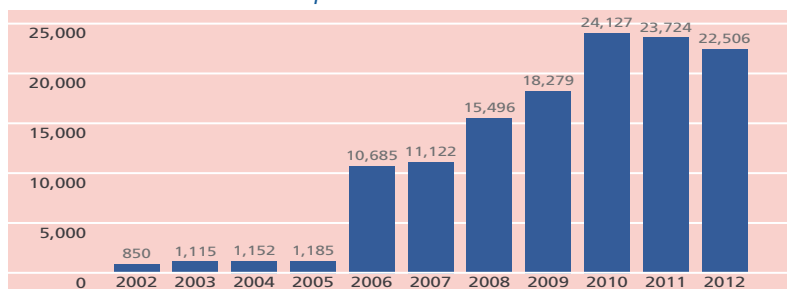


Table 1. Top 10 AEs by system organ class[^]

Ranking	System organ class	Number of reports	% of total number of AE terms quoted
1	Skin and Appendages Disorders e.g., angioedema, pruritus, rash	13,510	50.9
2	Body as a Whole - General Disorders e.g., anaphylaxis, fever, oedema, pain	4,782	18.0
3	Respiratory System Disorders e.g., coughing, shortness of breath, stridor, wheezing	1,843	6.9
4	Gastro-Intestinal System Disorders e.g., abdominal pain, diarrhoea, nausea, vomiting	1,384	5.2
5	Central and Peripheral Nervous System Disorders e.g., convulsions, dizziness, headache, oculogyric crisis	1,330	5.0
6	Urinary System Disorders e.g., face oedema, interstitial nephritis	998	3.8
7	Musculo-Skeletal System Disorders e.g., arthralgia, body aching, myalgia, rhabdomyolysis	405	1.5
8	Metabolic and Nutritional Disorders e.g., gout, azotaemia, increased creatine kinase	318	1.2
9	Heart Rate and Rhythm Disorders e.g., arrhythmia, bradycardia, QT prolongation, palpitation	302	1.1
10	Vascular (Extra-cardiac) Disorders e.g., flushing, vasculitis, stroke	297	1.1

[^] The system organ class refers to the adverse reaction terminology developed by the WHO.
(NB: More than one AE term may be described in an AE report)

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Table 2. Drugs suspected of causing serious adverse reactions

Description	WHO preferred term	Suspected active ingredient (the number in the bracket represents the number of times the drug has been implicated #)
Blood disorders	Agranulocytosis/ neutropenia	Amoxicillin (3), Carbimazole (3), Docetaxel (3), Clozapine (2), Imatinib (2)
	Leucopenia	Azathioprine (2), Cotrimoxazole (2), Imatinib (2)
	Pancytopenia	Imatinib (4), Azathioprine (2), Carbamazepine (2)
Skin disorders	Stevens-Johnson Syndrome (SJS)/ Toxic Epidermal Necrolysis (TEN)/SJS-TEN	Carbamazepine (12), Allopurinol (10), Cotrimoxazole (9), Coamoxiclav (9), Amoxicillin (5), Diclofenac (5), Lamotrigine (5), Omeprazole (4), Clarithromycin (3), Doxycycline (3), Naproxen (3), Phenytoin (3), Piperacillin and Tazobactam (3), Rifampicin (3), Gabapentin (3), Ceftriaxone (2), Esomeprazole (2), Etoricoxib (2), Isoniazid (2), Ibuprofen (2), Paracetamol (2), Pyrazinamide (2), Tetracycline (2), Vancomycin (2)
Body as a whole	Drug Hypersensitivity Syndrome	Allopurinol (12), Phenytoin (10), Cotrimoxazole (5), Abacavir (3), Carbamazepine (3), Vancomycin (3), Coamoxiclav (2), Diclofenac (2), Piperacillin and Tazobactam (2)
Hepatic disorders	Hepatitis /Hepatitis Cholestatic/Jaundice	Cotrimoxazole (5), Azathioprine (4), Simvastatin (3), Pyrazinamide (2), Sulfasalazine (2).

More than one suspected drug may be implicated in a single AE report. Only active ingredients implicated more than once are listed here.

Table 3. Top 8 vaccines, number of reports received and examples of serious VAEs

Ranking	Type of vaccine	Total number of reports received	Examples of some serious VAEs
1	Bacillus Calmette-Guerin (BCG)	100	Lymphadenitis (73), injection site abscess (1)
2	Hepatitis B	38	Vaccine failure (23), abscess (2), seizures (2), thrombocytopenia (1)
3	Measles, Mumps and Rubella	34	Seizures (17), Kawasaki disease (2), thrombocytopenia (2), Bell's Palsy (1), vaccine failure (1), Gianotti-Crosti Syndrome (1)
4	Pneumococcal conjugate	19	Kawasaki disease (5), seizures (4), thrombocytopenia (2), erythema multiforme (1), vaccine failure (1)
5	Measles, Mumps, Rubella and Varicella	16	Seizures (5), vaccine failure (5), Kawasaki disease (2), thrombocytopenia (2), severe papular erythematous rash (1)
6	Rotavirus	13	Intussusception (5), Kawasaki disease (2), haematochezia (1), seizure (1)
7	6-in-1 ⁺	12	Kawasaki disease (4), vaccine failure (2), seizures (1)
8	5-in-1 [*]	11	Seizures (6), Kawasaki disease (2), injection-site cellulitis (1)

⁺ 6-in-1 includes Diphtheria, Pertussis, Tetanus, inactivated Polio and Haemophilus influenza type B and Hepatitis B vaccines

^{*} 5-in-1 includes Diphtheria, Pertussis, Tetanus, inactivated Polio and Haemophilus influenza type B vaccines

Table 4. AEs associated with CHPs

Product Type	Hypersensitivity	Hepatic reactions	Others
Health supplements	88	6	1
Chinese Proprietary Medicines	4	5	4
Other traditional medicines	7	9	31 (including 20 caused by adulterated products)
Total	99	20	36

Caveat for interpreting the AE figures:

AE reports describe an adverse reaction (AR) that has occurred in association with a drug but does not necessarily mean that the drug has been determined to be the cause of the AR. Many other factors need to be taken into account in assessing causal relationships and these include the presence of underlying diseases and medical conditions and the possible contribution of concomitant medicines. It is worthwhile to note that the volume of AE reports for a particular drug may be influenced by the extent of use of the product, publicity, nature of reactions and other factors which vary over time. Therefore the reports should not be used to determine or measure the frequency of an AR.

under the National Childhood Immunisation Schedule. Thirty-two (11%) reports involved more than one vaccine. The vaccines commonly reported to cause AEs in children are listed in Table 3.

Since early 2010, HSA's Vigilance Branch has worked with KK Women's and Children's Hospital on active surveillance of paediatric VAEs. Hospital admissions were screened daily for AEs following immunisation and possible VAEs were reported, which contributed to the majority of the reports HSA received in the paediatric population from 2010 to 2012. Potential safety signals picked up were promptly shared through alerts in the HSA ADR News bulletin, including suppurative lymphadenitis with BCG vaccine and vertical transmission of hepatitis B despite immunoprophylaxis.

AEs associated with complementary health products (CHPs)

There were a total of 155 AE reports associated with CHPs including Chinese Proprietary Medicines, health supplements and other traditional medicines. These reports were broadly classified into four categories based on AEs reported and tabulated in Table 4.

Out of 155 reports, 99 were suspected hypersensitivity reactions and 20 were hepatic AEs. 80% of the hypersensitivity reactions were reported to be associated with glucosamine preparations and presented as rash, pruritus and angioedema. In many of the cases describing hepatic reactions, it was difficult to ascertain a definitive causality between the suspected products and hepatic reactions due to confounding factors such as concomitant medications and pre-existing medical conditions of the patients. Furthermore, herbs were often used in various combinations, doses and duration, making it difficult to isolate the component(s) that might have been responsible for the hepatic reactions.

Twenty AEs were caused by adulterated CHPs, which were tested to contain mainly drugs used to treat erectile dysfunction (e.g., sildenafil), corticosteroids, NSAIDs, antihistamines, and/or diuretics. Most products were marketed for relieving pain or sexual enhancement/vigour. Three press releases were issued in 2012 to alert members of the public not to consume these adulterated products. The press releases can be accessed from the HSA website at www.hsa.gov.sg.

Conclusion

It is through the vigilant efforts of our healthcare professionals and the well-developed IT infrastructure that has enabled Singapore to retain its ranking as the leading country in terms of the number of reports per million inhabitants that was submitted to the WHO's Uppsala Monitoring Centre.

HSA would like to take this opportunity to thank all healthcare professionals for their active participation in the AE monitoring programme. Your invaluable support and contribution is imperative to the continued partnership in the prompt detection of potential safety signals related to health products and actions taken to safeguard public health.

Bupropion and possible increased risk of congenital cardiovascular malformations

HSA would like to inform healthcare professionals of the potential risk of congenital cardiovascular malformations associated with the use of bupropion during the first trimester of pregnancy.

Bupropion is a selective inhibitor of the neuronal re-uptake of catecholamines, dopamine and noradrenaline, and is indicated for the treatment of depressive illness (Wellbutrin SR®, GlaxoSmithKline Pte Ltd), as well as an adjunct in smoking cessation (Zyban®, GlaxoSmithKline Pte Ltd).

Potential risk of congenital cardiovascular malformations

Data from a recent epidemiological study,¹ along with findings from other studies, showed a possible increased risk of congenital cardiovascular malformations following bupropion exposure during pregnancy. However, the findings and types of cardiovascular defects observed across the studies were not consistent. One study reported a potential increased risk of certain congenital cardiovascular malformations such as ventricular septal defects and left outflow tract heart defects following maternal exposure to bupropion in the first trimester of pregnancy,² while other published data did not find an increased risk when all types of congenital cardiovascular malformations were considered as a group.³

The results of these studies are summarised below.

- An analysis of case-controlled data from the Slone Epidemiology Center Birth Defects Study (7,913 infant cases of cardiac defects and 8,611 controls) did not find a statistically significant increased risk of left outflow tract heart defects with maternal bupropion use (n=2; adjusted odds ratio [AOR]=0.4; 95% CI=0.1, 1.6). However, a statistically significant association was observed for ventricular septal defects (n=17; AOR=2.5; 95% CI=1.3, 5.0) following the use of bupropion alone during the first trimester.¹
- In a retrospective case-control analysis using data from the National Birth Defects Prevention Study (12,383 case infants and 5,869 control infants), a statistically significant association was observed between the occurrence of a left outflow tract heart defects in the infant and self-reported maternal bupropion use in early pregnancy (n=10; AOR=2.6; 95% CI= 1.2, 5.7). However, no association was observed between maternal bupropion use and any other type of cardiac defects or with all categories of heart defects combined.²
- A retrospective, managed-care database study (7,005 infants) using United Healthcare data showed that infants exposed to bupropion during the first trimester were not at greater risk for all forms of congenital malformations (AOR=0.95; 95% CI=0.62, 1.45) or cardiovascular malformations (AOR=0.97; 95% CI=0.52, 1.80) when compared to infants exposed to other antidepressants during the first trimester. There was also no increased risk observed for all forms of congenital malformations (AOR=1.00; 95% CI=0.57, 1.73) or cardiovascular malformations (AOR=1.07; 95% CI=0.48, 2.40) in infants exposed to bupropion during the first trimester as compared to those exposed to bupropion outside the first trimester.³

HSA's advisory

To date, HSA has not received any local reports of congenital cardiovascular malformations associated with the use of bupropion.



HSA is working with the company to strengthen the precautions on its use in pregnancy and updating the pre-clinical safety data sections of the local package inserts for all bupropion-containing products to warn of the potential risk of congenital cardiovascular malformations following bupropion exposure. A Dear Healthcare Professional Letter has been issued in November 2012 to highlight the potential risk of congenital cardiovascular malformations associated with the use of bupropion during pregnancy.⁴

Healthcare professionals are advised to be aware of this potential risk when prescribing bupropion to women who are planning to become pregnant or who are pregnant, and

to weigh the option of alternative treatments. Should bupropion be considered the treatment of choice in women of child-bearing potential, healthcare professionals are encouraged to inform patients of the potential risk of congenital cardiovascular malformations associated with its use and to emphasise the importance of using an effective birth control method. Healthcare professionals are encouraged to report adverse reactions associated with the use of bupropion to the Vigilance Branch of HSA.

References

- 1 GSK Protocol 115433. *Bupropion and Cardiac Birth Defects* (Slone Epidemiology Centre).
- 2 *Am J Obstet Gynecol* 2010; 203: e1-6
- 3 *Pharmacoepidemiol Drug Saf* 2007; 16: 474-84
- 4 HSA website. Dear Healthcare Professional Letters (DHCPL)

Reminder on the safer use of NSAIDs

In the year 2012, HSA reviewed a total of 22,506 local ADR reports associated with the use of health products. Of the top 30 most commonly reported active ingredients suspected to cause ADRs, seven belong to the class of nonsteroidal anti-inflammatory drugs (NSAIDs).

Although skin and allergic reactions (e.g., rash, periorbital oedema, and angioedema) occurred in most of the ADRs reported, there are other known significant risks that this class of drug may pose, particularly cardiovascular and renal events such as heart attack, stroke and acute renal failure. HSA would like to remind healthcare professionals to adhere to the following precautions which have been recommended by its Product Vigilance Advisory Committee (PVAC) to minimise the risks associated with the use of NSAIDs:

- 1 All NSAIDs should be prescribed at the lowest effective dose and the duration of treatment should be periodically reviewed and kept as short as possible
- 2 All NSAIDs should not be used perioperatively in patients who have recently undergone coronary artery bypass graft (CABG) surgery and revascularisation procedures
- 3 All NSAIDs should be prescribed with care in elderly patients because of the possible risk of renal toxicity

Healthcare professionals are also encouraged to report any adverse reactions suspected to be related to the use of NSAIDs to the Vigilance Branch of HSA.



Levothyroxine and potential risk of fractures

An increase in the risk of fractures associated with the use of levothyroxine has been observed in a recent study.

Levothyroxine (Euthyrox®, Merck Pte Ltd) has been licensed locally since May 1998 for the treatment of benign euthyroid goitre and the prophylaxis of relapse after surgery for euthyroid goitre. It is also indicated as a substitution therapy in hypothyroidism, a concomitant therapy during anti-thyroid medicinal treatment of hyperthyroidism and a suppression therapy in thyroid cancer. Other brands of levothyroxine include Eltroxin® (A. Menarini Singapore Pte Ltd), Thyrosit® (Joyson Pte Ltd) and Levothyroxine sodium for injection 500mcg/vial (United Italian Trading Corporation (Pte) Ltd).



Potential risk of fractures

In a recent large study examining the risk of fractures in patients on levothyroxine, a strong dose-response relation between levothyroxine treatment and increased risk of fracture was observed.¹ This was a nested case-control study involving 213,511 adult levothyroxine users, with a mean age of 82 years, who were followed up for a mean duration of 3.8 years. Of these users, 22,236 (10%) experienced at least one fracture during follow-up.

Outcomes of the study found that current and recent past levothyroxine use were associated with a significantly increased risk of any fractures when compared to remote levothyroxine useⁱⁱ. Their respective adjusted odds ratio (AOR) were 1.88 (95% CI=1.71, 2.05) and 1.33 (95% CI=1.19, 1.48). Among current levothyroxine users, a higher risk of any fractures was observed for high (>0.093 mg/day) and medium (0.044 to 0.093mg/day) cumulative

doses of levothyroxine when compared to low (<0.044mg/day) cumulative doses. Their respective AOR were 3.45 (95% CI=3.27, 3.65) and 2.62 (95% CI=2.50, 2.76).

Local situation and HSA's advisory

HSA has not received any local reports of fractures associated with the use of levothyroxine and is currently monitoring this safety signal.

Healthcare professionals should be aware that long-term suppressive doses of levothyroxine therapy has been associated with increased bone resorption and reduced bone mineral density, especially in post-menopausal women.^{2,3} Currently, there is limited information on the effect of levothyroxine on bone mineral density in the local package inserts (PIs) of levothyroxine.

The PIs for all levothyroxine products will be further strengthened with this safety information.

Healthcare professionals are also advised to take into consideration the above safety information when prescribing levothyroxine to their patients and to prescribe the minimum dose necessary to achieve the desired clinical and biochemical response. Additionally, they are encouraged to report any adverse reactions or fractures associated with the use of levothyroxine to the Vigilance Branch of HSA.

- i Recent past treatment is defined as discontinuation of levothyroxine within 15 to 180 days of index date
- ii Remote treatment is defined as discontinuation of levothyroxine more than 180 days before index date

References

- 1 *BMJ* 2011; 342: d2238
- 2 *J Clin Endocrinol Metab* 1991; 72: 1184-8
- 3 *J Med Assoc Thai* 1996; 79: 563-7

Answers to AE case in focus: Test yourself

a) Yes, it could be drug-induced pneumonitis. Possible mechanisms for adverse pulmonary effects secondary to drugs include direct oxidative injury, pulmonary vascular damage or immune system-mediated injury. The likelihood of developing drug-induced pulmonary disorders remains largely unpredictable and idiosyncratic.

b) Nitrofurantoin

c) Yes. Notify HSA when you suspect there is a causal association between the drug taken and the adverse event experienced by the patient. Reporting an adverse event does not necessarily mean that there is a definite link between the event and the drug.

Pulmonary adverse reactions associated with nitrofurantoin present in acute and chronic forms. Acute pulmonary reactions occur 1 in 5,000 first administrations, and affect mainly women aged 40–50 years. The acute presentation is typically characterised by hypersensitivity-type features and occurs one to two weeks after initiation of nitrofurantoin, with a recurrence within minutes to hours following the administration of subsequent doses. Chronic pulmonary reactions occur 10 to 20 times less frequently than acute reactions, and tend to involve older persons. They may develop after six months or longer of nitrofurantoin therapy and may lead to interstitial lung disease and pulmonary fibrosis.

From 1993 to 31 December 2012, the Vigilance Branch of HSA has received six pulmonary ADR reports associated with nitrofurantoin, describing adverse events such as dyspnoea, wheezing, alveolitis fibrosing and acute lung injury. These pulmonary ADR reports form 4% of the local ADR reports associated with nitrofurantoin received during the same time period, which is lower than that reported in other international ADR monitoring databases. For example, respiratory disorders accounted for 34% of all nitrofurantoin-associated ADR reports received by New Zealand's Centre for Adverse Reactions Monitoring.¹

Pulmonary adverse reactions associated with nitrofurantoin are possible and should be considered when patients present with serious pulmonary symptoms such as shortness of breath following nitrofurantoin therapy. Patients who have been prescribed nitrofurantoin, either for a short course or as a long-term prophylactic therapy, should be advised to report serious pulmonary reactions to their physicians.

HSA encourages healthcare professionals to report any adverse reactions suspected to be related to the use of health products to the Vigilance Branch. Your support of the safety monitoring programme is invaluable in our partnership to safeguard public health.

Reference

- 1 <http://www.medsafe.govt.nz/profs/PUarticles/nitrofurant.htm>

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

Rivaroxaban (Xarelto®, Bayer (South East Asia) Pte Ltd) has been registered in Singapore since November 2008 for the prevention of venous thromboembolism in patients undergoing total hip replacement (THR) or total knee replacement surgery (TKR). In March 2012, the registered indication for Xarelto® was extended to include prevention of stroke and systemic embolism in subjects with non-valvular atrial fibrillation, as well as for treatment of deep vein thrombosis (DVT) and the prevention of recurrent DVT and pulmonary embolism (PE).

Recently, a review of the ADR reports received by the Netherlands Pharmacovigilance Centre, Lareb, raised a possible signal of lack of efficacy with Xarelto® for the prevention of VTE in adult patients undergoing elective hip or knee replacement surgery.¹ The reports from HSA's ADR database have not shown a similar trend for inefficacy and the safety signal observed in the Netherlands could be due to stimulated reporting, i.e. reporters are more likely to report possible adverse events of new drugs as compared to older drugs. Nonetheless, HSA would like to update healthcare professionals with this information and encourage continued safety monitoring of this anticoagulant.

Information from Netherlands Pharmacovigilance Centre, Lareb

As of March 2012, Lareb had received 48 ADR reports related to the use of rivaroxaban. Of these, 31 were reported as serious and the most frequently reported serious ADRs were bleeding events. There were also eight reports of PE associated with the use of rivaroxaban, which indicated a possible lack of efficacy in certain patients. Of these eight reports, four were confirmed with Computed Tomography (CT) scan. In comparison, the number of PE reports associated with rivaroxaban was disproportionately higher than that for low molecular weight heparin (LMWH) products, which were much more commonly

used than rivaroxaban. There were nine PE reports for nadroparin, four for dalteparin, and none for both enoxaparin and tinzaparin. Hence, Lareb has assessed that attention to lack of drug effect manifested through the occurrence of PE is warranted when using rivaroxaban following hip or knee replacement surgery.

Findings reported in literature

Neuman *et al* performed a systematic review and meta-analysis to evaluate the benefits and harm of oral direct factor Xa inhibitors (rivaroxaban, apixaban, edoxaban, YM150, TAK442, betrixaban and LY517717)

versus LMWH in patients undergoing THR or TKR.² In this study, no significant difference in non-fatal PE was found between factor Xa inhibitors and LMWH.

Local situation

Since 2008, HSA has received 20 ADR reports associated with the use of rivaroxaban. Among these cases, there were two cases that were related to drug inefficacy. These included one case of intracardiac thrombus (concomitant disease of left ventricular systolic dysfunction and dilated cardiomyopathy) where the indication was not reported and one case of stroke reported with the use of rivaroxaban for prevention of stroke and non-central system systemic embolism. The other ADRs were mainly due to haemorrhage, a known adverse effect associated with rivaroxaban.

HSA's advisory

HSA continues to monitor for reports of PE associated with rivaroxaban although there is no report of PE locally. Healthcare professionals are advised to monitor their patients for possible lack of efficacy. Healthcare professionals are also encouraged to report any adverse reactions suspected to be related to the use of rivaroxaban to the Vigilance Branch of HSA.

References

- 1 Netherlands Pharmacovigilance Centre Lareb Quarterly Newsletter, 4th quarter of 2012 NR8
- 2 Ann Intern Med 2012; 156: 710-9

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