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Adverse Drug Reaction News

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Domperidone and risk of cardiac arrhythmia and sudden cardiac death

Domperidone has been registered as a Prescription-Only Medicine (POM) in Singapore since 1989 as Motilium® suspension 1mg/ml and Motilium® Tablet 10mg, by Janssen, a division of Johnson & Johnson Pte Ltd. Currently, there are 11 other generic domperidone products available. Domperidone is indicated for dyspeptic symptom complex often associated with delayed gastric emptying, gastro-oesophageal reflux and oesophagitis as well as for nausea and vomiting. Domperidone may also be supplied by pharmacists as a POM with exemptions for supply without a prescription* when used for the relief of postprandial symptoms of excessive fullness, nausea, epigastric bloating and belching occasionally accompanied by epigastric discomfort and heartburn, at a maximum daily dose of 40mg.

Concerns about the cardiac safety of domperidone surfaced in the early to mid-1980s with reports of cardiac arrest, ventricular arrhythmias, and sudden death associated with the use of the intravenous formulation of domperidone, which was most often administered with other medications with known cardiac side effects. As a result, intravenous domperidone was withdrawn from the market in 1985. More recently, several epidemiological studies describing an association of oral domperidone with an increased risk of serious ventricular arrhythmia (SVA) or sudden cardiac death (SCD) were published.[1-5] These studies also suggest the increased risk is observed only among those who use oral domperidone at higher doses (>30mg/day)[1], and those who are more than 60 years old.[2]

Summary of studies that investigated cardiac risk of oral domperidone

1 Nested case-control study using the Saskatchaewan Health Electronic Database in Canada[1]

A case-control study nested in a retrospective cohort evaluated the combined risk of SVA and SCD in users of domperidone compared with users of proton pump inhibitors (PPIs), or non-users of these medications.

There were 83,212 individuals in the exposure cohort with the first dispensing of domperidone and/or a PPI between 1990 and 2005 (41,153 domperidone, 41,700 PPI and 359 both medications). From this exposure cohort, 49 SVA and 1,559 SCD cases were identified (mean age 79.4 years, females 52.9%, diabetes 22.3%) and 6,428 matched controls. The adjusted odds ratio (OR) for SVA/SCD with current domperidone use compared with non-use was (1.59, 95% CI: 1.28-1.98), or compared with current PPI use was (1.44, 95% CI: 1.12-1.86).

In stratified analyses, adjusted ORs were numerically higher in males, those more than 60 years old, and non-diabetics.

2 Domperidone and ventricular arrhythmia or SCD: a population-based case-control study in the Netherlands[2]

Another case-control study conducted between 1996 and 2007 in a longitudinal general practice research database in the Netherlands included patients aged ≥18 years without cancer in the source population. In this study, there were 1,366 cases (62 VA and 1,304 SCD) and matched 14,114 controls. Of all cases, ten patients were current domperidone users at the index date and all presented with SCD. The matched, unadjusted OR of domperidone and SCD was 3.72 (95% CI 1.72, 8.08). Daily doses >30 mg were associated with a significant increased risk of SCD (adjusted OR 11.4 [95% CI 1.99, 65.2]). The effect of domperidone on non-fatal VA was not demonstrated due to the absence of exposed cases.

* *Exemptions for supply of POM without prescription is a new initiative to facilitate public access to commonly used medicines. Such medicines may be supplied without a prescription by pharmacists if they are deemed by HSA to be sufficiently safe for use with reduced medical supervision. More information is available at the HSA website.*

Actions taken by the European Medicines Agency (EMA)[6]

Based on the assessment of the data from the studies described earlier, the EMA's Pharmacovigilance Working Party (PhVWP), recommended further updates to the product label to reflect the current information on the risk of sudden cardiac death, particularly in patients >60 years old and in patients taking daily doses of >30mg, and emphasised that domperidone should be used at the lowest effective dose in adults and children. The PhVWP also recommended that the marketing authorisation holder conduct an additional well-designed, high-powered epidemiological study on the association between domperidone and cardiac disorders, with particular emphasis on dose to further clarify this risk.

Local Situation

Currently, the recommended dose for domperidone in adults and adolescents is 10 to 20mg to be taken three to four times per day, with a maximum dose of 80mg daily

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Good Manufacturing Practices (GMP) deficiencies at Ben Venue Laboratories Inc, USA

This is an update regarding the recently identified deficiencies in the area of Good Manufacturing Practices (GMP) at the manufacturing site of the contract manufacturer, Ben Venue Laboratories Inc. (BVL) located in Bedford, Ohio, United States. A recent assessment by various regulators, including the US Food and Drug Administration (FDA) and Health Canada (HC) of the BVL manufacturing site had identified deficiencies in BVL's GMP, which may have an impact on the quality of the products manufactured there.

Background

BVL is a contract manufacturer of various injectable and inhalational medicinal products. Recently, a joint GMP inspection of the BVL site by regulators from the United Kingdom, France and the US had identified several short-comings in their quality-management systems, particularly in relation to the aseptic filling process in the North complex of the Ben Venue facility. The deficiencies in the quality assurance could potentially have an impact on the quality of products manufactured at the BVL manufacturing site. In late November 2011, Ben Venue announced the voluntary shutdown of its manufacturing and distribution facilities and that it will investigate the GMP issues identified by the regulators. The supply of all BVL manufactured products have ceased since the shutdown of the BVL manufacturing and distribution facilities.

Local Situation and Advisory

Healthcare professionals have been updated by HSA on the GMP deficiencies of BVL and the potential impact it may have on the quality of the affected BVL manufactured products. Additionally, actions taken to address the products manufactured at the BVL manufacturing site are as follows:

1 *BVL manufactured products that have an alternative manufacturing site*

HSA has suspended the supply of all registered medicinal products manufactured by BVL that have alternative manufacturing sources eg, Velcade 3.5mg Injection® (bortezomib), Busulfex Injection® (busulfan), diluent for Torisel® Concentrate (temsirolimus). To ensure that the ongoing supply of these affected medicinal products continues to meet the needs of local patients, HSA had worked with the affected product licence holders to initiate the supply of the affected products from alternative manufacturing sources. All existing BVL manufactured stocks of these medicinal products were also replaced with supplies sourced from the alternative manufacturing site.

2 *BVL manufactured products that do not have an alternative manufacturing site*

For BVL manufactured medicinal products that do not have an alternative manufacturing source but had been identified to be critical for patients' needs, eg, Caelyx® (liposomal doxorubicin), existing stocks should only be used to complete treatment that has been initiated and no new patients should be initiated on Caelyx® treatment until further notice. Physicians were advised to consider other treatment alternatives.

HSA is monitoring the situation and will ensure the affected products meet our regulatory requirements before being allowed back into the local market. Healthcare professionals are advised to report any adverse reactions suspected to be associated with the use of products manufactured by BVL to the Vigilance Branch and to include the relevant clinical details of the adverse reactions and batch numbers of the affected product.

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Domperidone and risk of cardiac arrhythmia or sudden cardiac death

while that for children and infants is 0.25 to 0.5mg/kg three to four times a day (up to a maximum of 2.4mg/kg but no more than 80mg per day).[7]

To date, HSA has not received any adverse drug reaction (ADR) reports relating to serious ventricular arrhythmias and sudden cardiac death. Most of the ADR reports were minor reactions pertaining to skin rash.

HSA's actions and advisory

This safety issue was reviewed by the Vigilance Branch in 2009 and early 2010. Janssen had initiated package insert updates to reflect SVA and SCD under the "Undesirable effects-postmarketing" as follows:

> *"An increase in the risk of serious ventricular arrhythmias and sudden cardiac death has been reported in some epidemiology studies. Due to the limitations of these data, risk factors and the exact frequency of these adverse reactions could not be defined."*

HSA is currently working with relevant product licence holders to update the package inserts of domperidone products to reflect the current information on the risk of SVA and SCD associated with the use of the product.

Healthcare professionals should be aware of these risks and be cautious, particularly when treating high risk patients with domperidone eg, those who have existing prolongation of cardiac conduction intervals like QTc and patients with significant electrolyte disturbances or underlying cardiac diseases such as congestive heart failure. When supplying domperidone as a POM with exemptions for supply without prescription, pharmacists are advised to check their patient's medical history and avoid dispensing domperidone to patients with underlying cardiac disorders. They may wish to advise patients with underlying cardiac disorders to consider alternative medicines or to seek advice from their doctors on the suitability of domperidone.

References

1 *Drug Saf. 2010; 33: 1003-1014*
2 *Pharmacoepidem and Dr S 2010; 19: 881-888*
3 *Br J Clin Pharm 2007; 63(2): 216-23*
4 *Eur Heart J 2005; 26(19): 2007-12*
5 *Brit J Clin Pharmaco 2009; 68(5): 743-51*
6 *PhVWP Monthly Report 27 October 2011*
7 *Singapore package insert for Motilium® (domperidone)*

Early termination of aliskiren study due to adverse events

HSA would like to update healthcare professionals on the recent early termination of the Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE) as the results showed that there was no benefit with aliskiren and that there were more cases of stroke, renal complications, hyperkalemia and hypotension in patients who received aliskiren compared with patients who received a placebo.

Aliskiren is available in Singapore as a single-ingredient (Rasilez®, Novartis) and in combination with hydrochlorothiazide (Rasilez® HCT, Novartis). It is currently indicated to treat primary hypertension either as a monotherapy or in combination with other antihypertensives (diuretics, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and calcium channel blockers).

About the ALTITUDE study

The ALTITUDE study was a placebo controlled phase III trial aimed at evaluating the potential benefits of aliskiren, in addition to conventional therapy including an ACE inhibitor or an ARB, in reducing the risk of CV and renal events, when used in type 2 diabetic patients at high risk for fatal and non-fatal CV and renal events. This is the first long-term investigation of aliskiren with a planned follow up period of four years and involved 8,606 diabetic patients with renal impairment and/or CV disease from 36 countries. The primary endpoint of the ALTITUDE study was the first occurrence of one of the following events: CV death, resuscitated sudden death, non-fatal myocardial infarction, non-fatal stroke, unplanned hospitalisation for heart failure, doubling of baseline serum creatinine concentration to above the upper limit of normal (sustained for at least one month), and onset of end stage renal disease or renal death. The secondary CV endpoint was the first occurrence of the above-mentioned CV outcomes while the secondary renal endpoint was the first occurrence of renal events.

ALTITUDE Interim results

In Dec 2011, the independent Data Monitoring Committee overseeing the study reviewed the second interim analysis for ALTITUDE. At that time, 69% of the projected total primary outcome events had been accrued. The results of this interim analysis are shown in ***Table 1***.[1]

Table 1. ALTITUDE Primary and secondary composite outcomes and each component outcome based on adjudicated events; time-to-event analysis in a randomised population

Variable	Aliskiren (N=4283)	Placebo (N=4296)	Total (N=8579)	HR	95% CI	P-value
Primary composite outcome	581 (13.6%)	542 (12.6%)	1123 (13.1%)	1.09	(0.97, 1.22)	0.1663
Secondary composite outcome – CV	444 (10.4%)	396 (9.2%)	840 (9.8%)	1.14	(0.99, 1.30)	0.0664
Secondary composite outcome – renal	166 (3.9%)	180 (4.2%)	346 (4.0%)	0.93	(0.76, 1.15)	0.5178

The emergence of an imbalance in primary and CV composite endpoints was observed only after 18-24 months of treatment. There was an increased risk of primary outcome events associated with aliskiren with a hazard ratio (HR) of 1.09 (95% CI 0.97- 1.22). However, based on an assumption of a 15% risk reduction (HR = 0.85) of primary outcome events in the original study design, the conditional probability that the study would demonstrate benefit at the end of the trial was $p < 0.0001$.[2] Hence, the Data Monitoring Committee concluded from this interim analysis that the study patients were unlikely to achieve the primary objective of the study to benefit from aliskiren.

There was also a higher incidence of adverse events related to fatal or non-fatal stroke (2.6% vs. 2.0%), renal serious adverse events, i.e. renal impairment, acute renal failure, chronic renal failure, renal failure (4.7% vs. 3.3%), hyperkalaemia (36.9% vs. 27.1%) and hypotension (18.4% vs. 14.6%) in the aliskiren group as compared to placebo.

In view of the futility in meeting the final endpoint and the substantial safety concerns highlighted through the preliminary analyses of the interim results,

the Data Monitoring Committee recommended that all subjects cease treatment with aliskiren. The information available at present is preliminary and additional analyses from ALTITUDE by Novartis are ongoing.

Actions taken by the European Medicines Agency (EMA)[3]

Following a review of data and analyses from the ALTITUDE study, alongside all data from other studies and spontaneous reports of suspected adverse drug reactions associated with aliskiren, the EMA's Committee for Medicinal Products for Human Use (CHMP) had concluded that the benefit-risk balance of Rasilez and combination products containing aliskiren remains positive for the treatment of essential hypertension but requested the inclusion of a contraindication against the use of aliskiren in patients with diabetes or moderate to severe renal impairment (GFR<60ml/min/1.73m^2) who take ACE inhibitors or ARBs as well as to include a warning that the combination of aliskiren with an ACE inhibitor or ARB is not recommended in all other hypertensive patients patients because adverse outcomes cannot be excluded.

HSA's actions and advisory

To date, HSA has received 14 suspected adverse reaction reports associated with the use of aliskiren, of which four involved CV events (one case of hypotension, myocardial infarction and stroke and three cases of hypotension).

In view of the interim findings from ALTITUDE, HSA would like to remind healthcare professionals to review their patients on aliskiren therapy. As aliskiren or aliskiren-containing fixed combination products should not be used in combination with ACE inhibitors or ARBs in diabetic patients, healthcare professionals are advised to stop aliskiren-based treatments and not initiate new aliskiren treatment in diabetic patients who are taking an ACE inhibitor or an ARB. Alternative antihypertensive treatment should be considered as necessary.

A Dear Healthcare Professional Letter (DHCPL) was issued by Novartis, in consultation with HSA, in January 2012 to update on the safety concerns and above recommendations. HSA is currently working with Novartis to update the package inserts of Rasilez® and Rasilez® HCT to reflect this new information. Healthcare professionals are encouraged to report all suspected adverse reactions associated with aliskiren to the Vigilance Branch of HSA.

References

1 *http://hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2012/rasilez_hpc-cps-eng.php*
2 *Data Monitoring Committee's recommendation letter for ALTITUDE, dated 14 Dec 2011*
3 *http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/public_health_alerts/2012/02/human_pha_detail_000055.jsp&mid=WC0b01ac058001d126&jsenabled=true*

Analysis of Adverse Event (AE) Reports for Year 2011

Singapore has taken the world lead in terms of the number of valid reports per million inhabitants that was submitted to the World Health Organisation (WHO) global database from 2006 to 2011. This is according to the October 2011 report published by WHO's Uppsala Monitoring Centre (see ***Chart A***).

In the year 2011, the Vigilance Branch (VB) of HSA received a total of 30,175 local reports of adverse events (AE) suspected to be related to health products. Of these, 23,724 were captured into the national database as valid reports. Reports lacking important details such as names of suspected drugs and AE descriptions are invalid reports and will not be captured into the national AE databse as they cannot be assessed for causality

Chart B provides a breakdown of the number of valid reports captured in our AE database from the years 2006 to 2011 based on date of receipt. There is a steady increase in number of AE reports captured in our local database as more healthcare institutions routed their reports electronically to VB via the ADR/drug allergy reporting module in the Critical Medical Information Store (CMIS).

Types of health products involved

Majority of the reports analysed were associated with pharmaceuticals/biologics (98%) followed by vaccines (1.3%). Complementary medicines including Chinese Proprietary Medicines, health supplements and other traditional medicines account for 0.5% of the reports.

Demographics

Chinese patients constituted the highest proportion (67.4%) of AE reports, followed by Malays (11.8%) and Indians (7.4%). This is consistent with the Singapore population demographics. There were more reports of AEs occurring in females (58.3%) than in males. The patients were mainly between 20 and 69 years of age with the highest frequency at 50 to 59 years.

Source of AE reports

The majority of the reports processed was from healthcare professionals working in the government clinics (50.7%) followed by public hospitals (45.6%), pharmaceutical companies (1.3%) and private clinics/hospitals (0.9%).

Review of AE reports

The top 10 most commonly reported active ingredients suspected to cause adverse events are listed in ***Table 1***. The most commonly reported AEs include rash, periorbital oedema, angioedema, pruritus, coughing, urticaria and dyspnoea.

Grouping by System-organ Class

Most of the AEs reported were skin-related disorders (52.4%), followed by those affecting the body as a whole (i.e. general disorders such as pain, fever, oedema) (17.5%), and respiratory disorders (6.7%). Please refer to ***Table 2*** for the full listing of top 10 AEs based on system-organ classification.

Drugs suspected of causing serious blood, hepatic and skin reactions are listed in ***Table 3***.

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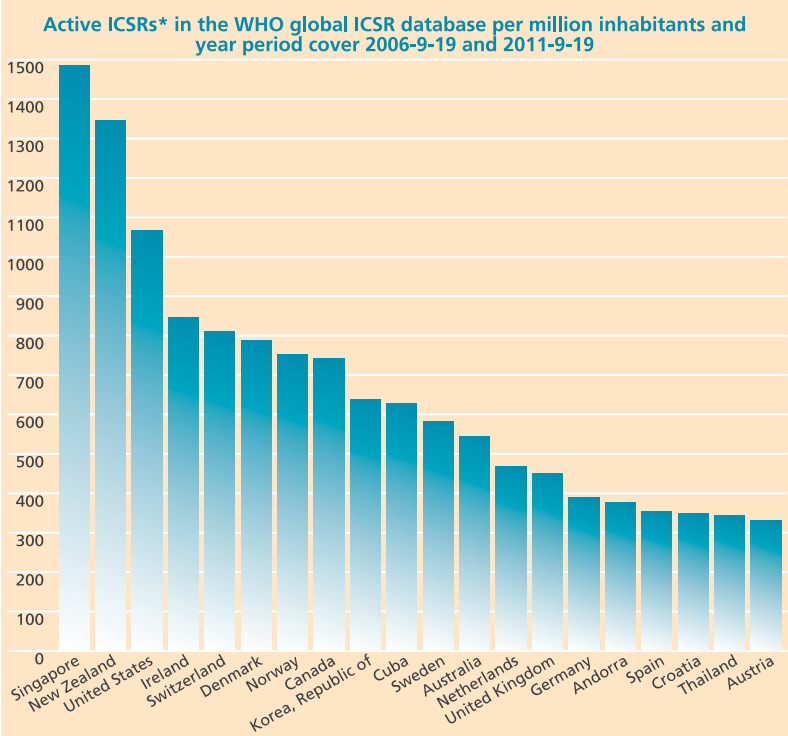
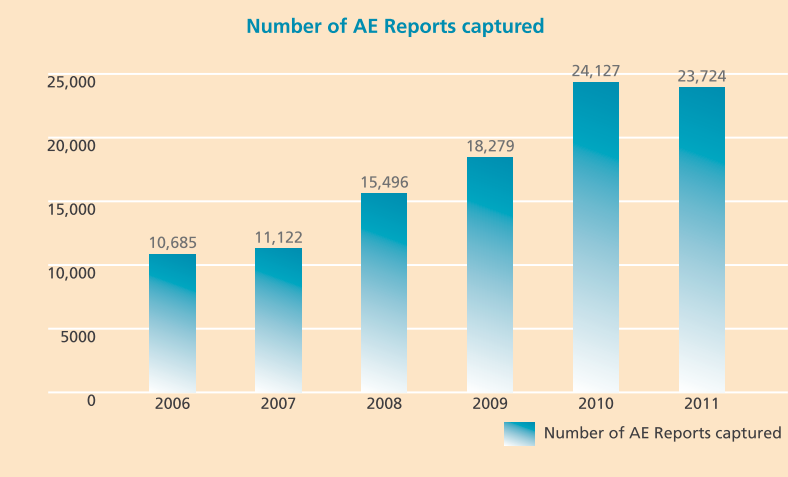
Chart A: Reporting rates (per million inhabitants and year) to the UMC



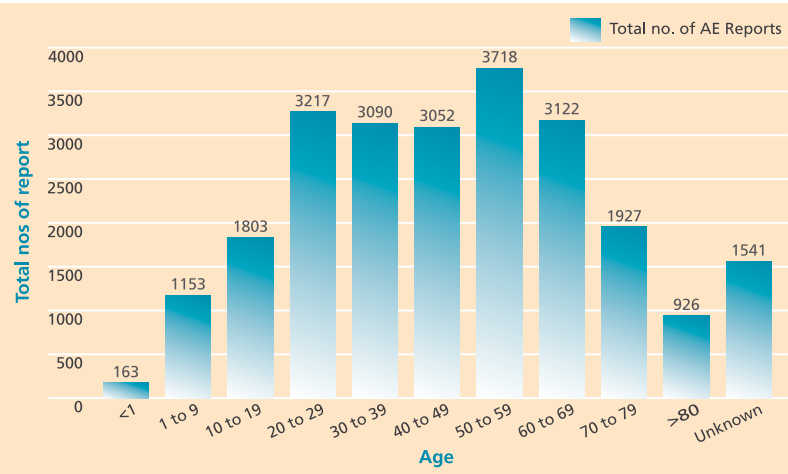
* *Individual Case Safety Reports*

*[**Ref:** Uppsala Montoring Centre, Uppsala Reports 55, October 2011, page 6]*

Chart B: No. of AE reports captured into AE database from Year 2006 to 2011 based on date of receipt



Demographics



■ ***A good quality Adverse Event (AE) report should include details such as "Indication of drug used", "Outcome of Adverse Event (AE)" and "Time to onset of AE".*** ■

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Analysis of Adverse Event (AE) Reports for Year 2011

Table 1: Top 10 drugs (by active ingredients) suspected of causing AEs

Top	Active ingredient	No. of reports (**)
1	Amoxicillin	2,398
2	Paracetamol	1,534
3	Diclofenac	1,372
4	Cotrimoxazole	1,086
5	Ibuprofen	977
6	Aspirin	967
7	Naproxen	924
8	Enalapril	692
9	Mefenamic acid	653
10	Simvastatin	600

** *More than one suspected drug may be implicated in an AE report.*

*Table 2: Top 10 AEs by system-organ classes^*

Top	System organ class	No. of reports (%≠)
1	Skin & appendages	14,583 (52.4)
2	Body as a whole	4,883 (17.5)
3	Respiratory	1,862 (6.7)
4	Gastrointestinal	1,419 (5.1)
5	Nervous	1,335 (4.8)
6	Urinary	956 (3.4)
7	Musculoskeletal	449 (1.6)
8	Metabolic & nutritional	411 (1.5)
9	Heart	337 (1.2)
10	Vascular	265 (1.0)

^ *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)*

≠ *Percentage of total no. of AE terms quoted*

Table 3: 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	Carbimazole (4), Cisplatin (4), Carbamazepine (3), Doxorubicin (3), Vancomycin (3), Alemtuzumab (2), Bevacizumab (2), Fludarabine (2), Meropenem (2), Oxaliplatin (2), Piperacillin And Tazobactam (2)
	Leucopenia	Azathioprine (5), Carbamazepine (3), Sulfasalazine (2)
	Pancytopenia	Ceftriaxone (2), Piperacillin And Tazobactam (2)
	Thrombocytopenia	Oxaliplatin (15), Valproate (5), Piperacillin And Tazobactam (4), Cotrimoxazole (3), Heparin (3), Rifampicin (3), Calcium Folinate (2), Capecitabine (2), Carbamazepine (2), Enoxaparin (2), Fluorouracil (2), Linezolid (2), Mumps Measles Rubella And Varicella (2), Peginterferon Alfa-2a (2), Piperacillin (2), Sulfasalazine (2).
Skin disorders	Stevens-Johnson syndrome (SJS)/ toxic epidermal (TEN)/SJS-TEN	Carbamazepine (17), Cotrimoxazole (10), Phenytoin (8), Allopurinol (7), Amoxicillin (6), Paracetamol (6), Vancomycin (5), Coamoxiclav (4), Etoricoxib (4), Omeprazole (4), Tetracycline (4), Cefazolin (3), Lamotrigine (3), Piperacillin And Tazobactam (3), Sulfasalazine (3), Ampicillin (2), Ciprofloxacin (2), Diclofenac (2), Erythromycin (2), Fluconazole (2), Meropenem (2), Quetiapine (2), Strontium Ranelate (2).
Body as a whole	Drug Hypersensitivity Syndrome	Allopurinol (6), Cotrimoxazole (6), Phenytoin (5), Diclofenac (2), Erythromycin (2), Isoniazid (2), Rifampicin (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 4: Top 5 vaccines, number of reports received and examples of serious VAEs

Ranking	Type of vaccine	Total no. of reports received	Examples of some serious VAEs
1	Bacillus Calmette-Guerin (BCG)	87	Lymphadenitis (42), injection site abscess (4)
2	Hepatitis B	24	Idiopathic thrombocytopenia (2) seizures (3)
3	Pneumococcal	22	Kawasaki disease (6) lack of efficacy (3) seizures (3)
4	Rotavirus	16	Kawasaki disease (2), idiopathic thrombocytopenia (2) intussuception
5	6-in-1+	15	Kawasaki disease (3), idiopathic thrombocytopenia (2), seizures (2)

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

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.

Analysis of vaccine adverse event (VAE) reports

A total of 216 suspected VAE reports were received, of which 135 reports (63%) were classified as serious. 179 reports (83%) involved children less than 12 years of age which corresponds with the age-group of vaccinees under the National Childhood Immunisation Schedule. Of the 216 reports, 33 (15%) reports involved more than one vaccine. The top five suspected vaccines more commonly reported to cause AEs in children are listed in ***Table 4***.

Analysis of AE reports on Complementary Health Products (CHP)

There were 112 AE reports processed for CHP in 2011. Of these, 22 adulterated products were detected as a result of follow-up investigation. These led to six press releases being issued by HSA to alert the public against taking these harmful products.

The most commonly reported AE was Cushing's Syndrome due to the presence of corticosteroids detected in 70% of the adulterated products. Other commonly reported AE include hepatotoxicity (ranging from mild elevation of liver enzymes to hepatitis) which accounted for 12% of the reports. No clustering of cases or association with any pain killer product was identified for these cases.

48% of the reports on CHP are associated with glucosamine containing products with the majority (75%) reporting non-serious AE such as rash, urticaria and periorbital oedema.

Concluding remarks

The Vigilance Branch would like to take this opportunity to thank healthcare professionals for their active participation in the national adverse event monitoring programme of health products. We encourage healthcare professionals to submit good quality AE reports which is imperative in facilitating prompt detection of potential health product-related safety signals leading to appropriate actions taken to safeguard public health.

A good quality Adverse Event (AE) report should include details such as "Indication of drug used", "Outcome of Adverse Event (AE)" and "Time to onset of AE".

Medication errors arising from brand name confusion between Pradax® (dabigatran etexilate) and Plavix® (clopidogrel hydrogen sulphate) in Canada

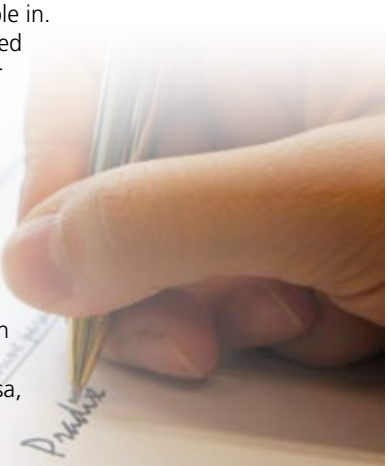
There have been incidences of medication errors which occurred in Canada arising from the confusion of brand names between Pradax® (dabigatran etexilate) from Boehringer Ingelheim (Canada) Ltd. and Plavix® (clopidogrel bisulfate) from Sanofi-Aventis Canada Inc. In Singapore, although the brand name of dabigatran is slightly different, HSA would like to highlight this issue to healthcare professionals so that similar errors can be avoided here.

Dabigatran is marketed under the brand name of Pradaxa® in Singapore since August 2009 by Boehringer Ingelheim Singapore Pte Ltd. It is an oral anticoagulant (direct thrombin inhibitor) indicated for the prevention of venous thromboembolic events in adult patients following total hip or knee replacement surgery and for prevention of stroke and systemic embolism in patients with atrial fibrillation, in whom anticoagulation is appropriate. Pradaxa® is available in 75mg, 110mg and 150mg capsules.

Clopidogrel (Plavix®, Sanofi-Aventis Singapore Pte. Ltd) is an oral platelet aggregation inhibitor locally licensed since June 1998, for the prevention of atherothrombotic events in adult patients with myocardial infarction, ischaemic stroke, acute coronary arterial syndrome or established peripheral arterial disease. Plavix® is available as 75mg tablets.

Information from Health Canada

In November 2011, Health Canada issued a safety advisory on the risk of potential patient harm associated with brand name confusion between Pradax® and Plavix®. Since January 2011, a total of five Canadian cases, associated with drug name confusion between Pradax® and Plavix®, have been received by Boehringer Ingelheim (Canada) Ltd. and Health Canada, including one case resulting in patient harm (non-serious bleeding after a medical procedure). These mix-ups have been associated with similarities in the sound of the tradenames, the spelling of the tradenames and the similar strengths that they are available in. The fact that they are both used in patients with cardiovascular disorders also lead to a higher likelihood of mix-up.



HSA's advisory

Although both products are anti-thrombotic agents, they have different mechanisms of action, indications dosing regimens, and drug interaction profiles. Receiving Pradaxa® instead of Plavix®, or vice versa, may result in inappropriate treatment of the condition as well as the wrong dosage being administered. This may have significant risks including increased risk of bleeding, stroke, systemic embolism, venous thromboembolic events (VTE), atherothrombotic events or other unknown medical outcomes.

HSA would like to highlight this potential risk to the healthcare professionals when prescribing, dispensing and administering these two drugs. As recommended in the MOH Medication Safety Practice Guidelines & Tools, healthcare professionals are encouraged to use the generic names of the drugs when prescribing to avoid any potential confusion.

References

1 *http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2011/plavix_2_hpc-cps-eng.php*
2 *http://www.moh.gov.sg/content/dam/moh_web/HPP/all_healthcare_professionals/Medication%20Safety.pdf*

Phasing-out of serratiopeptidase-containing preparations as medicinal products

HSA has conducted a re-evaluation of the benefit-risk of serratiopeptidase for its current approved clinical uses. Serratiopeptidase is currently approved in Singapore for anti-inflammatory and expectorant uses.

Serratiopeptidase products were first registered in 1991 shortly after the implementation of Singapore's drug registration system. While the clinical evidence then was sufficient to support the registration of these products based on the regulatory standards at that point in time, new data from recent clinical trials has shown that it does not provide significant clinical benefit over the use of placebo for the approved indications.

Re-evaluation of serratiopeptidase as a medicinal product

The re-evaluation exercise by HSA was undertaken following the voluntary withdrawal of the innovator product Danzen® (serratiopeptidase) tablets in Japan in February 2011 by the drug company, Takeda. Based on the data submitted by various product licence holders, including clinical studies conducted by the proprietor as well as data from published clinical papers, HSA's present evaluation concluded that current available data could not sufficiently demonstrate and confirm the efficacy of serratiopeptidase for the approved clinical uses as the studies either failed to show statistically significant differences from placebo or were inadequate in terms of study design and methodology.

HSA's regulatory decision

On this basis, the HSA has taken the regulatory decision to phase out serratiopeptidase-containing preparations as medicinal products. Considering the long history of use in Singapore with minimal safety concerns, the phase-out process will follow a gradual approach to ensure that immediate impact on patients and industry stakeholders is minimised. With this, currently registered products will be allowed to continue their marketing authorisation until the respective product licence expires.

There are currently ten serratiopeptidase preparations registered as medicinal product in Singapore. Details of the specific product and the validity period of the respective product licence can be found on the HSA website using the "Online Information Search (Infosearch)" function at the weblink ***http://www.hsa.gov.sg/Infosearch***. The last product licence will expire in November 2012. Consequently, serratiopeptidase will be phased out as a medicinal product in Singapore.

Notwithstanding the regulatory decision taken on serratiopeptidase-containing medicinal products, serratiopeptidase is not precluded as an ingredient in other health products such as health supplements. Healthcare professionals may wish to contact the Pharmaceuticals and Biologics Branch of HSA at email: ***hsa_medprod_enquiry@hsa.gov.sg*** should you have queries on the above information.

■ ***A good quality Adverse Event (AE) report should include details such as "Indication of drug used", "Outcome of Adverse Event (AE)" and "Time to onset of AE".*** ■

Updates on the exemptions for supply of Prescription-Only Medicine (POM) without prescription

To facilitate public access to commonly used medicines, HSA has embarked on a biannual review to identify Prescription Only Medicines (POM) which may be supplied without prescription by pharmacists under exemptions where they are deemed sufficiently safe for use with reduced medical supervision. Three new POMs have been assessed to meet the criteria to be granted exemptions for supply without prescription as of 1 January 2012. There has also been an amendment to the current exemptions for ibuprofen solid and liquid oral preparations.

Table 1: Exemptions for supply of POM medicine without prescription with effect from 1 January 2012

1 *Desloratadine/Pseudoephedrine modified release oral solid dosage forms containing desloratadine 2.5mg and pseudoephedrine 120mg*
2 *Fexofenadine/Pseudoephedrine modified release oral solid dosage forms containing fexofenadine 60mg and pseudoephedrine 120mg*
3 *Ketotifen eyedrops not exceeding 0.25 mg/ml*

Amendment to exemptions for supply without prescription with effect from 1 January 2012

1 *Ibuprofen oral solid preparations containing not more than 200mg and oral liquid preparations not more than 100mg/5ml*

In this amendment, the exemptions for maximum daily dose and minimum age for ibuprofen have been included. Changes have also been made to the maximum supply of ibuprofen oral solid and liquid preparations.

Record Keeping

With effect from 1 February 2012, the requirement for mandatory record keeping of supply of P medicines and POM with exemptions for limited sale and supply without prescription has been fully implemented. This requirement is intended to better safeguard consumers who buy medicines from the pharmacist. The records also assist the pharmacist in following up with consumers should there be any issues concerning the use and quality of these medicines. To raise public awareness of this initiative, HSA has produced educational material to be displayed at pharmacies to inform the public on the need for record keeping.

In addition, the HSA Consumer guide on how drugs are regulated in Singapore has been updated, with a new link as follows: ***www.hsa.gov.sg/regulatingmedicines***

Pharmacists are encouraged to refer members of the public to this website for an overview of drug regulation. This weblink will also be displayed on the educational materials provided to members of the public.

All healthcare professionals are encouraged to report adverse reactions related to these medicines to the Vigilance Branch of HSA. For more information on reclassified medicines and POMs with exemptions for limited sale and supply without prescription, including downloadable Patient Information Leaflets (PILs), Frequently Asked Questions (FAQs) and mandatory recording requirements, please visit our website at: ***http://www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/western_medicines/reclassified_medicines.html.***

Cessation on production and commercialisation of Duxaril® (almitrine and raubasine)

Servier International has voluntarily ceased the production and commercialisation of Duxaril® as of end January 2012.

Duxaril® is a fixed dose combination of almitrine and raubasine that has been licensed locally since 29 May 1989 for the treatment of psychobehavioural disturbances associated with cerebral aging, namely intellectual disorders and psychological disorders. It is also indicated for suggested uses in chorioretinal and cochleovestibular disorders of ischaemic origin.

The cessation of production and commercialisation of Duxaril® was initiated worldwide in response to the re-evaluation of clinical studies involving Duxaril®, which showed a lack of statistical confirmation of efficacy of Duxaril® in improving cognitive function in patients with vascular cognitive impairment. No safety issues were identified from this re-evaluation study.

Servier (S) Pte Ltd had advised physicians in October 2011 to switch their patients on Duxaril® to alternative treatments.

Risk of dose-dependent QT prolongation with citalopram

Implementation of risk minimisation measures

HSA would like to update healthcare professionals on the risk minimisation measures that will be implemented to mitigate the risk of dose-dependent QT interval prolongation with citalopram. These measures include new dosing and warning recommendations.

Background

Citalopram is a selective serotonin reuptake inhibitor (SSRI) indicated for the treatment of depression and prevention of relapse/recurrence, panic disorder with or without agoraphobia, and obsessive-compulsive disorder. Two citalopram-containing products are registered in Singapore, with Cipram® (LF Asia Pharmaceutical Division) registered since 1992, and Ciram (Drug Houses of Australia) in January 2012.

In August 2011, the US Food and Drug Administration (FDA) notified healthcare professionals and patients that citalopram should no longer be used at doses greater than 40mg per day due to the risk of dose-dependent QT interval prolongation.[1] Studies also did not show a benefit in the treatment of depression at doses higher than 40mg per day.

The FDA evaluated the results of a thorough QT study* assessing the effects of 20mg and 60mg doses of citalopram against placebo on the QT intervals in adults (n=119). In the study, when compared to placebo, maximum mean prolongations in the individually corrected QT (QTc)** intervals were 8.5ms (90% CI 6.2–10.8) and 18.5ms (90% CI 16.0–21.0) for 20mg and 60mg citalopram, respectively. For 40mg citalopram, prolongation of the QTc interval was estimated to be 12.6ms (90% CI 10.9–14.3).

As a result of this thorough QT study and the FDA's analysis of post-marketing reports of QT interval prolongation and Torsade de Pointes associated with citalopram, the citalopram US product label was revised to include the new drug dosage and usage recommendations, as well as important safety information about the potential for QT interval prolongation and Torsade de Pointes (***Table 1***).[2]

Actions by other regulatory agencies

Other regulatory agencies, including the European Medicines Agency (EMA),[3] Australia Therapeutic Goods Administration (TGA),[4] UK Medicines and Healthcare products Regulatory Agency (MHRA)[5] and Health Canada,[6] have also issued new dosing recommendations for citalopram, with a maximum dose of 40mg daily in adults and 20mg daily in elderly and patients with reduced hepatic function. New warnings were also added to the product labels of citalopram-containing products.

Table 1: Summary of updated dosing and warning recommendations

■ Citalopram causes dose-dependent QT interval prolongation, which can cause Torsades de Pointes, ventricular tachycardia, and sudden death
■ Citalopram is not recommended for use at doses greater than 40mg per day because such doses cause too large an effect on the QT interval and confer no additional benefit
■ The maximum recommended dose is 20mg per day for patients with hepatic impairment, who are older than 60 years of age, who are CYP2C19 poor metabolisers, or who are taking concomitant cimetidine or other CYP2C19 inhibitors, because these factors lead to increased blood levels of citalopram, increasing the risk of QT interval prolongation and Torsade de Pointes
■ Citalopram is not recommended for use in patients with congenital long QT syndrome, bradycardia, hypokalaemia or hypomagnesaemia, recent acute myocardial infarction, or uncompensated heart failure. Citalopram use is also not recommended in patients who are taking other drugs that prolong the QT interval
■ Consider more frequent electrocardiogram (ECG) monitoring in patients for whom citalopram use is not recommended, but is, nevertheless, considered essential
■ Patients at risk for significant electrolyte disturbances should have baseline serum potassium and magnesium measurement, with periodic monitoring. Hypokalaemia and/or hypomagnaesemia may increase the risk of QTc prolongation and arrhythmia and should be corrected prior to initiation of treatment with periodic monitoring
■ Citalopram should be discontinued in patients found to have persistent QTc measurements greater than 500ms

* *A thorough QT study refers to a single trial intended to determine if a drug has a threshold pharmacologic effect on cardiac repolarisation, as detected by QT/QTc prolongation. Please refer to the following weblink for more information http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm129357.pdf.*

** *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.*

Local situation

To date, HSA has not received any local reports of QT prolongation associated with use of citalopram.

Following the FDA announcement, HSA initiated an evidence-based review regarding the maximum dose for citalopram, including a review of the thorough QT study reports used by the FDA to support their regulatory decision, and determined that a reduction in maximum dose to 40mg daily is warranted. HSA has been working with the companies to update the local package inserts for Cipram® and Ciram™ to reflect the new dosing and warning recommendations.

HSA's advisory

Healthcare professionals are advised to adhere to the new dosing and warning recommendations for citalopram. Patients should be advised to contact a healthcare professional immediately if they experience signs and symptoms of an abnormal heart rate or rhythm (eg, dizziness, palpitations or syncope) while taking citalopram. Healthcare professionals are also encouraged to report any suspected adverse reactions associated with the use of citalopram to the Vigilance Branch of HSA.

References

1 *http://www.fda.gov/Drugs/DrugSafety/ucm269086.htm*
2 *http://www.fda.gov/Drugs/DrugSafety/ucm297391.htm*
3 *http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/10/WC500117061.pdf*
4 *http://www.tga.gov.au/safety/alerts-medicine-citalopram-111104.htm#hp*
5 *http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON137769*
6 *http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2012/celexa_2_hpc-cps-eng.php*

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All website references were last accessed on 30 Mar 2012.