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Adverse Drug Reaction News

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An update on the risk of intussusception with rotavirus vaccines

In October 1999, the first marketed rotavirus vaccine (RotaShield®) was withdrawn in the United States (US) after studies suggested an elevated risk of intussusceptions (IS) which translated to nine additional cases of IS per 100,000 infants who received RotaShield®. Consequently, due to the concern with IS, large-scale clinical trials involving more than 60,000 infants for the new generation rotavirus vaccines, Rotarix®, (GlaxoSmithKline) and RotaTeq® (Merck Sharp & Dohme), were conducted to evaluate the risk of IS prior to licensure. As pre-registration safety studies may not always detect rare events, post-marketing studies to further evaluate the potential for IS were also being conducted. This article updates healthcare professionals on the recent findings from the post-marketing studies on the risk of IS with Rotarix® and RotaTeq®. Rotavirus vaccination is an optional vaccination in Singapore.

Post-marketing studies in Mexico and Brazil

A study was conducted by the Pan American Health Organisation and US Centres for Disease Control and Prevention to determine IS risk and health benefits of rotavirus vaccination in Brazil and Mexico.[1] The authors used case-series and case-control methods to assess the association between Rotarix® and IS. Infants with IS (n = 615) were identified through active surveillance at 69 hospitals (16 in Mexico and 53 in Brazil), and age-matched infants from the same neighbourhood (n = 2,050) were enrolled as controls. The infants were observed from the time they were 45 days of age until they were 245 days of age. The primary risk window was one to seven days after Rotarix® vaccination, but the authors also assessed the risk at the following additional timepoints: eight to 14 days, and 15 to 21 days after vaccination with both doses.

An increased risk of IS one to seven days after the first dose of Rotarix® was identified among infants in Mexico with both the case-series method (incidence ratio 5.3; 95% CI 3.0 - 9.3) and the case-control method (odds ratio 5.8; 95%CI 2.6 - 13.0). No significant risk was found after the first dose among infants in Brazil, but an increased risk by a factor of 1.9 to 2.6 was seen one to seven days after the second dose. In Mexico, a two-fold risk of IS after vaccination was also noted during the second and third weeks after dose two.

In conclusion, a combined annual excess of IS in Mexico (approximately one per 51,000 infants) and in Brazil (approximately one per 68,000 infants) and five deaths due to IS was attributable to Rotarix®. The authors also performed a benefit-risk analysis using existing epidemiologic and vaccination data to model the benefits and risks associated with having a vaccination program in Mexico and Brazil. Using this modelling, the vaccine was found to prevent approximately 80,000 hospitalisations and1,300 deaths from diarrhoea each year in these two countries.

An interim analysis of a similar study sponsored by GSK Biologicals[2] in a different population in Mexico also suggests an increased risk of IS in the 31-day period after the first dose, with a cluster of cases occurring during the first week after vaccination (relative risk 1.8; 99% CI 1.0 - 3.1).

Post-marketing studies in Australia

In Australia, two post-marketing studies were conducted to investigate whether Rotarix® and RotaTeq® are associated with an increased risk of IS.

The first study was conducted through the active surveillance of IS cases in four tertiary centres and a separate surveillance system involving national retrospective reporting of IS cases by paediatricians. This study found a four-fold increased risk of IS in babies within one week of being given the first dose of either vaccine, compared with historical data on hospitalisations coded as IS, but no overall increase in rates of IS up to the age of nine months.

Following this, a large self-controlled case series study using data on all hospitalised cases coded as IS from three Australian states was commissioned by the Australia Therapeutic Goods Administration (TGA). This study found a statistically significant four-fold increase

in the occurrence of IS in the first one to seven days following the first dose of either Rotarix® (relative risk 3.89; 95% CI 1.53 - 9.89) or RotaTeq® (relative risk 4.12; 95% CI 1.26 - 13.48) compared with other time periods after vaccination.

continued on Page 2

CONTENTS

continued from Page 1

■ **An update on the risk of intussusception with rotavirus vaccines** ■

This increase in risk translates to approximately two additional cases of IS occurring in every 100,000 first doses of vaccine administered, or six additional cases each year in children under 12 months of age in Australia.

Despite the small increase in risk of IS following the first dose of rotavirus vaccination, the TGA considers that the overall benefit-risk balance of both vaccines remains positive. In Australia, since the introduction of these vaccines into the National Immunisation Programme, emergency department visits for acute gastroenteritis and hospitalisations for rotavirus gastroenteritis in young children have reduced by over 70%.[3]

In December 2010, the Global Advisory Committee on Vaccine Safety to the World Health Organisation reviewed and debated the emerging data.[4] The Committee continues to recommend that rotavirus vaccination be administered to infants to prevent severe and potentially fatal rotavirus disease.

Local situation

Rotarix® and RotaTeq® have been licensed in Singapore since October 2005 and July 2007 respectively for the vaccination of infants six weeks and older against gastroenteritis due to rotavirus infection. To date, HSA has received a total of six cases of IS following receipt of rotavirus vaccines. Four of the reports were associated with Rotarix®*. Of these, two were associated with the second dose of Rotarix®, occurring on day four and day 18 after vaccination. The other two reports occurred five and seven days after first dose vaccination. For RotaTeq®, IS was associated with the second dose of the vaccine, occurring 18 days and four weeks after vaccination. All the patients have either recovered or were recovering at the time of reporting.

**The data provided should not be used to draw comparisons on the safety of different brands of rotavirus vaccines as this is confounded by factors such as extent of use.*

Regulatory actions by HSA and advisory to healthcare professionals

In early 2011, additional information has been added to existing "Postmarketing Experience" subsection under "Adverse Reactions" of the local package insert of Rotarix® to inform healthcare providers about the possible increased risk of IS in the 31 day time period after the first dose of Rotarix®. This information has also been included in the "Warnings and Precautions" section.

More recently, GSK has updated on an overseas report of a fatal case of IS following the second dose in a child who experienced IS after the first dose. HSA is currently working with GSK to strengthen the local PI to reflect this new contraindication.

As a precaution, healthcare professionals are advised to be vigilant of any symptoms indicative of IS (vomiting, palpable abdominal mass, abdominal pain, bloody stools, or diarrhoea) following vaccination with Rotarix® or RotaTeq®. Parents should be advised to seek treatment early if the child has vomiting, abdominal pain, blood in the stool or change in bowel movements at any time after vaccination, even if it has been several weeks since the last dose of the vaccine. Healthcare professionals are encouraged to report any adverse reactions suspected to be associated with rotavirus vaccines to the Vigilance Branch of HSA.

HSA will continue to closely monitor the safety profile of rotavirus vaccines and keep healthcare professionals updated on any new significant findings.

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3. *http://www.tga.gov.au/safety/alerts-medicine-rotavirus-110225.htm*
4. *http://www.who.int/vaccine_safety/topics/rotavirus/rotarix_and_rotateq/Dec_2010/en/index.html*

Counterfeit coloured contact lenses sold in Singapore

Recently, counterfeit contact lenses fraudulently labelled as "FreshLook® ColorBlends®" Contact Lenses from CIBA VISION were found to be distributed illegally by optical shops in Singapore. On testing, these products were found to be unsafe and of poor quality. These counterfeit contact lenses were sold for aesthetic purposes and for the correction of short-sightedness.

Dangers of using counterfeit lenses

The safety and quality of these counterfeit products cannot be ascertained as their manufacturing processes and conditions are unknown. Laboratory analyses of these counterfeit lenses by HSA and CIBA VISION have confirmed that they are unsafe, of poor quality and deficient in many aspects. The solution which the lenses were packaged in was found to contain *Pseudomonas aeruginosa*, which is known to cause severe eye infections. Additionally, the counterfeit lenses have lower water content and were thicker in the lens' centre compared to the genuine products. These defects would minimise the oxygen permeability of the lenses.

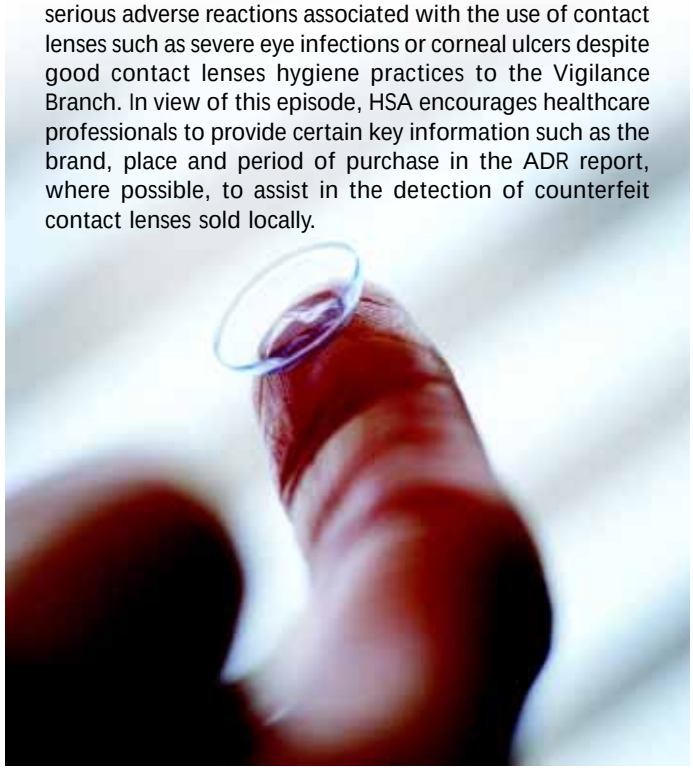
The use of a counterfeit product, in particular, one that is placed directly on the eye, may seriously affect the user's eyesight and also potentially lead to serious complications such as eye infections, corneal ulcers and blindness. Throbbing pain, redness of the eye and blurred vision are some examples of adverse reactions reported with the use of these counterfeit lenses.

HSA actions

Investigations and surveillance by HSA has detected five optical shops to be in possession of these counterfeit contact lenses. All counterfeit lenses from these shops have been seized. Further investigation has provided information relating to possible suppliers of the counterfeit coloured contact lenses and HSA officers are pursuing these leads.

HSA's advisory

Healthcare professionals are encouraged to report cases of serious adverse reactions associated with the use of contact lenses such as severe eye infections or corneal ulcers despite good contact lenses hygiene practices to the Vigilance Branch. In view of this episode, HSA encourages healthcare professionals to provide certain key information such as the brand, place and period of purchase in the ADR report, where possible, to assist in the detection of counterfeit contact lenses sold locally.



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Association of venous and arterial thromboembolism with thalidomide and lenalidomide (Revlimid®)

HSA would like to update healthcare professionals on the association of venous and arterial thromboembolic events with lenalidomide and thalidomide.

Thalidomide is an immunomodulatory agent with anti-angiogenic and anti-neoplastic properties. It is licensed in some countries for use in combination with dexamethasone or melphalan and prednisone in patients with multiple myeloma (MM). Although thalidomide is not registered locally, it had been made available on a named-patient basis for patients who have been assessed to have no suitable therapeutic alternatives.

Lenalidomide (Revlimid®, Celgene), a thalidomide analogue, has been licensed locally since June 2009 for use in combination with dexamethasone for the treatment of MM in patients who have received at least one prior therapy. In view of its potential teratogenic effects, the **RevAssure Programme[1] was implemented at the point of product licensure to minimise the risk of foetal exposure. Under this programme, healthcare professionals are required to fulfill certain conditions such as the need to obtain the patient's written informed consent to confirm their understanding of the risks associated with Revlimid®, provide appropriate counselling on effective contraception methods and to rule out pregnancy in women of childbearing potential before prescribing and dispensing Revlimid®.

*** Complete details of the RevAssure programme can be obtained from Celgene Pte Ltd*

Post-marketing data on venous and arterial thromboembolism

Although MM is an independent risk factor for thromboembolic complications, there has been evidence from post-marketing reports that both thalidomide and lenalidomide may further increase the risk of venous and arterial thromboembolic reactions in patients with MM.[2-4]

(A) Thalidomide

From a recent review of overseas post-marketing data, it was observed that patients treated with thalidomide had an increased risk of arterial thromboembolism in addition to the established risk of venous thromboembolism.

Approximately one third of all thromboembolic reactions reported in association with thalidomide were of arterial origin. The majority of these thromboembolic events were arterial MI (54.2%) or cerebrovascular events (19.8%).[2, 4]

Although the mechanisms involved in the pathogenesis of arterial thromboses remain unknown, the risk appears to be the greatest during the first five months of treatment. In addition, most patients presenting with venous or arterial thromboembolic events in association with thalidomide treatment have identifiable risk factors for thromboembolism.

(B) Lenalidomide

The combination of lenalidomide and dexamethsaone has also been associated with an increased risk of venous and arterial thromboembolism (predominantly deep vein thrombosis, pulmonary embolism, MI and cerebrovascular accident).[3]

A review of the Celgene pharmacovigilance database found that a total of 493 medically confirmed reports of arterial thromboembolic events associated with lenalidomide have been received. These reports showed a predominance of cardiac events (65% of reports) and 17% of the reports were contributed by cerebral vascular events, including transient ischaemic attacks. While a causal relationship between lenalidomide and arterial thromboembolic events cannot be excluded, the predisposing factors and mechanisms leading to MI have not been identified.

Of note was that majority of the patients with venous (>80%) and arterial (>60%) thromboembolic events were not documented to have received thromboprophylaxis. In addition, most of the patients with medically confirmed venous thromboembolic events had risk factors predisposing them to such events.

Local situation

As of 6 June 2011, HSA has received one suspected report of MI associated with the use of lenalidomide. This occurred in an 87 year-old female who had developed two episodes of non-ST elevation MI (NSTEMI) while taking lenalidomide for the treatment of MM. The patient first developed breathlessness due to pulmonary oedema caused by NSTEMI. The MI event was reported to have resolved following treatment and therapy with lenalidomide was continued. About a month later, the patient was re-admitted to hospital for life-threatening NSTEMI accompanied by acute pulmonary oedema and shortness of breath.

The local package insert for Revlimid® is being revised to include risk of arterial thromboembolism, in addition to the existing warning of the increased risk of venous thromboembolism associated with the use of the product.

HSA's advisory

Healthcare professionals are advised to take into consideration the above safety information, the presence of venous and arterial thromboembolic risk factors (eg, smoking, hypertension, hyperlipidaemia) as well as the need for thrombo-prophylaxis, when evaluating if their patients are suitable for treatment with thalidomide or lenalidomide.

Healthcare professionals are also advised to closely monitor their patients for signs and symptoms of thromboembolism and to inform their patients to seek immediate medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling.

Healthcare professionals are encouraged to report suspected cases of venous or arterial thromboembolic events associated with the use of thalidomide and lenalidomide to the Vigilance Branch of HSA.

References

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Dronedarone (Multaq®) and severe hepatic injury

HSA is alerting healthcare professionals to overseas cases of rare, but severe liver injury, including two cases of acute liver failure leading to liver transplant in patients treated with dronedarone.

Dronedarone (Multaq®, Sanofi-Aventis Singapore Pte Ltd), an anti-arrhythmic, has been licensed locally since August 2010. It is indicated to prevent recurrence of atrial fibrillation (AF) or to lower ventricular rate in clinically stable adult patients with a history of AF, or with current non-permanent AF.

Acute hepatic failure requiring transplantation

HSA was informed of several overseas case reports of hepatocellular liver injury and liver failure in patients treated with dronedarone. There were two cases of liver failure that required liver transplantation that occurred in October and November 2010. Both patients were females, aged 69 and 72 years old and their explanted livers showed evidence of extensive hepatocellular necrosis.

The first patient who underwent liver transplant had underlying intermittent AF, arterial hypertension and stable coronary artery disease. She was taking dronedarone for a total of 4.5 months. Two weeks prior to hospitalisation, she experienced increased exhaustion and tiredness. A week prior to admission, dronedarone was discontinued and at the time of admission, the patient was noted to have jaundice, coagulopathy, transaminitis and hyperbilirubinaemia, which progressed to hepatic encephalopathy over the next nine days. Liver transplantation was performed after all other causes concerning liver damage had been excluded.

The second patient had a medical history of paroxysmal AF and Sjögren's syndrome. Six months following initiation of dronedarone, the patient developed weakness, abdominal pain, coagulopathy, transaminitis and hyperbilirubinaemia. Liver tests and transplant work-up performed did not reveal any alternative causes of liver damage and liver transplantation was performed successfully.

Although both patients were taking concomitant medications such as anti-hypertensives (eg, amlodipine), cholesterol-lowering medications (eg, simvastatin) and anticoagulants (eg, warfarin), a causal relationship with dronedarone could not be excluded.

International regulatory actions

On 14 January 2011, the US FDA[1] issued a drug safety communication to alert healthcare professionals and patients about reports of rare, but severe liver injury, including the two cases of liver transplant in patients treated with dronedarone. Information about the potential risk of liver injury was added to the "Warnings and Precautions" and "Adverse Reactions" sections of the dronedarone package inserts (PI).

Similar regulatory actions were also taken by the European Medicines Agency[2] and Health Canada[3] where the PI for Multaq® has been strengthened to include warnings of liver injury.

Local regulatory actions

To date, HSA has not received any local reports of liver injuries associated with dronedarone.

A Dear Healthcare Professional Letter[4,5] has been issued on 8 June 2011 to inform healthcare professionals of liver injuries reported in patients treated with dronedarone. The local PI and physician educational materials for Multaq® have also been updated to include warnings on the risk of liver injury.

Healthcare professionals are advised to counsel their patients to look out for signs and symptoms of liver injury or toxicity such as anorexia, nausea, vomiting, fever, malaise, fatigue, right upper quadrant pain, jaundice, dark urine, or itching and to periodically monitor serum liver enzymes and bilirubin in patients taking dronedarone.

Healthcare professionals are also encouraged to refer to the latest prescribing information in the PI[6] of Multaq® when prescribing the drug to patients and to report any liver-related adverse reactions associated with the use of dronedarone to the Vigilance Branch of HSA.

References

1. *FDA Drug Safety Communication: Severe liver injury associated with the use of dronedarone. http://www.fda.gov/Drugs/DrugSafety/ucm240011.htm*
2. *European Medicines Agency: Benefit-risk review of Multaq started http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2011/01/news_detail_001187.jsp&murl=menus/news_and_events/news_and_events.jsp&mid=WC0b01ac058004d5c1&jsenabled=true*
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5. *MOH-Health Professionals Portal. http://www.hpp.moh.gov.sg*
6. *HSA website. Inforsearch for Singapore package inserts http://eservice.hsa.gov.sg/prism/common/enquirepublic/SearchDRBProduct.do?action=load*

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Risk of hypomagnesaemia associated with long-term use of proton pump inhibitors

HSA would like to inform healthcare professionals that emerging data has shown that proton pump inhibitors (PPIs) may cause hypomagnesaemia if taken for prolonged periods of time. This applies especially to treatment duration with PPIs that exceed one year. Low serum magnesium levels can result in serious adverse events including tetany, arrhythmias and convulsions. This risk may be increased for patients on concomitant drugs known to deplete magnesium, such as digoxin and diuretics. Patients who develop hypomagnesaemia, besides requiring magnesium supplementation, may also need to discontinue their PPI therapy.

PPIs are indicated for a variety of conditions such as gastro-oesophageal reflux disease, acid-related dyspepsia, gastric and duodenal ulcers, and reflux oesophagitis. PPIs include omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole.

Regulatory actions taken by the US Food and Drug Administration (FDA)

In March 2011, the US FDA announced that it would be adding information about the potential risk of hypomagnesaemia with prolonged PPI use into the package inserts of all prescription PPIs.[1] This warning arose from the FDA's review of this safety issue, which focused on 38 cases in the US Adverse Event Reporting System (AERS) and an additional 15 cases reported in the literature. The data reviewed by FDA suggested an association between hypomagnesaemia-related serious adverse events and prolonged PPI use. However, since hypomagnesaemia has not been formally known to be associated with the use of PPIs, this condition is likely under-recognised and under-reported. As such, the available data is insufficient to quantify an incidence rate for hypomagnesaemia with PPI therapy.

Most cases of hypomagnesaemia occurred after a year of treatment with PPIs, with some reported in adult patients after taking PPIs for three months. In approximately one-quarter of the cases reviewed, magnesium supplementation alone did not improve low serum magnesium levels and the PPI had to be discontinued. The median time required for magnesium to normalise was one week after discontinuing the PPI, whereas the median time to develop hypomagnesaemia again after re-challenging the PPI was two weeks.

Serious adverse events observed with hypomagnesaemia included tetany, seizures, tremors, carpo-pedal spasm, atrial fibrillation, supraventricular tachycardia, and abnormal QT interval. Hypomagnesaemia also produces impaired parathyroid hormone secretion which may lead to hypocalcaemia. The mechanism responsible for hypomagnesaemia associated with long-term PPI use is currently unknown. However, it may be related to changes in the intestinal absorption of magnesium.

HSA's actions and advisory

To date, HSA has not received any local reports of hypomagnesaemia associated with PPI use, but this could likely be due to under-recognition of this adverse effect. HSA is working with the licence holders of PPI products to strengthen the local package insert for all PPIs to include warnings that reflect the above safety issue. In addition, HSA recommends that healthcare professionals may consider monitoring magnesium levels prior to the initiation of PPI treatment and periodically in patients expected to be on prolonged PPI treatment or those who take PPIs with medications such as digoxin or drugs that may cause hypomagnesaemia (eg, diuretics).

For patients taking digoxin concomittantly, periodic monitoring of serum magnesium level is especially important because hypomagnesaemia can increase myocardial sensitivity to cardiac glycosides.

In most patients, treatment of hypomagnesaemia may require magnesium replacement and discontinuation of the PPI. Patients should be advised to seek immediate care from a healthcare professional if they experience arrhythmias, tetany, tremors, or seizures while on prolonged treatment.

Healthcare professionals are also strongly encouraged to report any adverse reactions suspected to be associated with PPIs to the Vigilance Branch of HSA.

References

1. http://www.fda.gov/Drugs/DrugSafety/ucm245011.htm

Recent product safety-related articles published on HSA website

HSA's electronic publications of product safety-related articles are available via the weblink: http://www.hsa.gov.sg.

All healthcare professionals are encouraged to visit HSA's website to access the latest product safety information.

1. Association of terbutaline with maternal deaths and serious cardiovascular adverse events in preterm labour (12 Apr 2011)
2. HSA updates on the test results for phthalates of Augmentin® Oral Suspension available locally (10 June 2011)
3. HSA updates on the voluntary recall of "Oral-B Tooth and Gum Care Mouth Rinse" and "Oral-B Tooth and Gum Care Alcohol-Free Mouth Rinse" by Procter & Gamble (Singapore) (15 July 2011)
4. Benzocaine and the risk of methaemoglobinaemia (4 Aug 2011)
5. HSA's advisory on the use of pioglitazone (8 Aug 2011)

Updates on reclassified medicines in Singapore

Medicines in Singapore are classified as Prescription Only Medicine (POM), Pharmacy only (P) medicine or General Sales List (GSL) medicine with varying levels of access control according to their risk profiles. In general, a medicine would be reclassified from POM to P (eg, Aleve® containing naproxen sodium 220mg) or P to GSL (eg, Miconazole dermatological preparations not exceeding 2%) when it had been deemed by regulatory authorities to be sufficiently safe and appropriate for use with reduced medical supervision. Conversely, a medicine would be reclassified from P to POM or GSL to P/POM when there is evidence to suggest that a P or GSL medicine should be used under greater medical supervision.

In order to facilitate access by the public to commonly used medicines, HSA has embarked on a biannual review of POM medicinal products to identify those which may be supplied without prescription by pharmacists under exemptions where they are deemed sufficiently safe for use with reduced medical supervision. In the recent review, eight POM active ingredients have been assessed to meet the criteria to be granted exemptions for supply without prescription as of 1 July 2011.

Enhancing the appropriate and safe use of Reclassified Medicines

Additionally, HSA has developed tools to ensure that all P medicines and medicines granted exemption for supply of POM without prescription are judiciously dispensed to members of the public. One such tool is record-keeping mandated for the supply of these medicines. This has been implemented in stages since 1 April 2011 and with effect from 1 February 2012, mandatory recording is required for all P medicines, or POMs granted exemption for supply without prescription by pharmacists. Another tool co-developed with the pharmacy professional body is the publication of Patient Information Leaflets (PIL) for these medicines, that is available at HSA's website. Pharmacists are strongly encouraged to refer to these PILs when counselling their patients on the use and side effects of the medicine.

Table 1: Exemptions for supply of POM medicine without prescription with effect from 1 July 2011

1) Triamcinolone acetonide topical paste containing not more than 0.1%
2) Bromhexine oral solid preparations containing not more than 8mg
3) Bromhexine oral liquid preparations containing not more than 4mg/5ml
4) Ambroxol oral solid preparations containing not more than 30mg
5) Ambroxol oral liquid preparations containing not more than 30mg/5ml
6) Desloratadine oral solid preparations containing not more than 5mg
7) Desloratadine oral liquid preparations containing not more than 0.5mg/5ml
8) Fexofenadine oral solid preparations containing not more than 120mg

The monitoring of the above list of medicines for any adverse reactions is crucial especially during its first few years on the market as a POM with exemptions for supply without prescription. All healthcare professionals are encouraged to report adverse reactions related to these medicines to the Vigilance Branch of HSA. For more information on the list of reclassified medicines and their regulatory conditions of use, downloadable PILs and mandatory recording requirements, please visit our website at: *http://www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/western_medicinesreclassified_medicines.html.*

Label updates on fluoroquinolones and QT prolongation

HSA would like highlight the recent changes made to the labelling of fluoquinolones relating to the risk of QT interval prolongation. Fluoroquinolones are broad spectrum antibiotics that are used to treat a wide range of indications such as the treatment of infections of the urinary tract, respiratory tract, skin and soft tissue, bones and joints, and abdominal cavity. Fluoroquinolones licensed locally include ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin, ofloxacin, lomefloxacin, gatifloxacin and pefloxacin.

Review by the Committee for Medicinal Products for Human Use (CHMP) in EU[1]

QT interval prolongation is a known potential adverse effect associated with the use of fluoroquinolones.[2] The CHMP of the European Medicines Agency (EMA) recently performed a review of QT prolongation related to fluoroquinolones, taking into consideration data from *in vivo* studies, *in vitro* electrophysiological studies and post-marketing data. From this review, the CHMP concluded that fluoroquinolones may be stratified into three groups depending on their potential for inducing QT interval prolongation. This was based on the fact that fluoroquinolones with a greater potential for inducing QT interval prolongation could lead to *torsades de pointes*, especially in the presence of risk factors such as hypokalaemia, hypomagnesaemia, bradycardia or congenital or acquired prolongation of the QT interval.

HSA's assessment and actions

HSA has reviewed this safety issue in the local context, taking into consideration the data reviewed by EU CHMP. To date, HSA has not received any reports of QT prolongation associated with use of the above mentioned fluoroquinolones. HSA is currently working with drug companies to update the package inserts of all oral and intravenous formulations of fluoroquinolones to strengthen the warnings regarding the potential of QT interval prolongation associated with its use. The level of warning required for each fluoroquinolone will vary according to its risk for inducing QT interval prolongation. A summary of labelling updates required for each risk category of fluoroquinolones is listed in Table 1 *on page 7*.

continued on Page 7

Topiramate (Topamax®) and risk of birth defects

There has been new evidence suggesting an increase in the risk of cleft lip and cleft palate in infants born to women treated with topiramate monotherapy during pregnancy.

Topiramate (Topamax®, Johnson & Johnson Pte Ltd) is an anti-epileptic drug licensed locally since 1998 for the treatment of certain types of seizures in patients with epilepsy and for the prevention of migraine headache in adults.

US Food and Drug Administration (FDA)

In March 2011, FDA announced new evidence indicating that prenatal exposure to topiramate increases the risk of the development of oral defects such as cleft lip and cleft palate in the foetus.[1]

The new data is derived from the North American Anti-epileptic Drug (NAAED) Pregnancy Registry, showing an increased risk of oral clefts in infants exposed to topiramate monotherapy during the first trimester of pregnancy. The prevalence of oral clefts was found to be 1.2% in infants exposed to topiramate *in utero* as compared to a prevalence of 0.39% to 0.46% in infants exposed to other anti-epileptic drugs (AEDs). This is contrasted with the prevalence of 0.12% observed in infants born to mothers without epilepsy or treatment with AEDs. The relative risk of oral clefts in topiramate-exposed pregnancies was found to be 9.6 (95% CI 3.6 - 25.7) in the NAAED Pregnancy Register as compared to the background risk in the population.

Data from the United Kingdom Epilepsy and Pregnancy Register also reported a similar increased prevalence of oral clefts (3.2%) among infants exposed to topiramate monotherapy *in utero*. This translates to a 16-fold increase in the risk of oral clefts in topiramate-exposed pregnancies when compared to the background incidence (0.2%).

Topiramate was previously classified by the FDA as a Pregnancy Category C drug due to inadequate human data on foetal risk. With new human data indicating evidence of human foetal risk in acquiring oral clefts, topiramate has been reclassified to Pregnancy Category D.

Local regulatory actions

To date, HSA has not received any local reports of birth defects associated with the use of topiramate. The existing "Pregnancy and Lactation" section of the local package insert for Topamax® will be strengthened to reflect this new safety information. A Dear Healthcare Professional Letter (DHCPL)[3,4] has been issued in August 2011 to inform healthcare professionals of this new safety information, as well as the information that has been included in the package insert.

HSA's advisory

Healthcare professionals are advised to weigh the benefits and risks of prescribing topiramate to women of childbearing potential. Should topiramate be considered the treatment of choice, healthcare professionals are encouraged to inform patients about the increased risk of oral clefts when topiramate is used during the first trimester of pregnancy and to emphasise the importance of using an effective birth control method.

Healthcare professionals are also encouraged to report all adverse reactions suspected to be associated with the use of topiramate to the Vigilance Branch of HSA.

References

1. *FDA Drug Safety Communication: Risk of oral clefts in children born to mothers taking Topamax (topiramate). http://www.fda.gov/Drugs/DrugSafety/ucm245085.htm*
2. *FDA Package insert for Topamax® http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020505s042.020844s0361b1.pdf*
3. *HSA website. Dear Healthcare Professional Letters (DHCPL). http://www.hsa.gov.sg/DHCPL*
4. *MOH-Health Professional Portal (HPP). http://www.hpp.moh.gov.sg*

continued from Page 6

■ **Label updates on fluoroquinolones and QT prolongation** ■

HSA's advisory

Healthcare professionals are encouraged to take into consideration the potential of a fluoroquinolone to cause QT prolongation when selecting this choice of therapy for their patients, especially in patients with risk factors. Healthcare professionals are also encouraged to report any adverse reactions suspected to be associated with the use of fluoroquinolones to the Vigilance Branch of HSA.

References

1. *European Medicines Agency Monthly report from the PhVWP December 2010 meeting. http://www.ema.europa.eu/ema/index.jsp?curl=search.jsp&q=fluoroquinolones+and+QT+prolongation&btnG=Search&murl=&mid=*
2. *The Merck Manuals. http://www.merckmanuals.com/professional/sec14/ch170/ch170f.html?qt=fluoroquinolones&alt=sh#sec14-ch170-ch170f-322i*

Table 1: Risk category of fluoroquinolones

A. Summary of labelling updates for fluoroquinolones with a potential for inducing QT interval prolongation – moxifloxacin
- contraindications in patients with conditions predisposing them to QT interval prolongation
- warnings and precautions regarding the prolongation of QT interval and QT-prolongation related clinical conditions
- updated list of medicinal products which may interact with the fluoroquinolones and contribute to an additive effect on QT interval prolongation
- where available, the frequency of occurrence of QT interval prolongation and QT interval prolongation related clinical conditions
- recommendations for symptomatic treatment and ECG monitoring in the event of overdose.

B. Summary of labelling updates for fluoroquinolones with a low potential for inducing QT interval prolongation – levofloxacin, ciprofloxacin, norfloxacin and ofloxacin
- warnings and precautions when used in patients with conditions predisposing to QT interval prolongation
- use with caution in patients on other drugs known to prolong QT intervals
- include the following as adverse reactions: ventricular arrhythmia and *torsades de pointes*, ECG QT prolonged
- recommendations for symptomatic treatment and ECG monitoring in the event of overdose

C. Summary of labelling updates for fluoroquinolones with a very low potential for inducing QT interval prolongation or for which there is insufficient information available – pefloxacin and lomefloxacin
- warnings and precautions to highlight that QT interval prolongation has been associated with the fluoroquinolone class of antibiotics

■ ***Healthcare professionals are reminded to complete the Risk Communication survey so as to help us improve the way we bring product safety information to you!*** ■

Serious skin reactions associated with strontium ranelate (Protos®)

HSA would like to alert healthcare professionals on the occurrence of suspected serious skin reactions associated with the use of strontium ranelate (Protos®) locally. Protos® has been registered in Singapore since July 2006 for the treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures.

Local reports

As of 31 July 2011, the Vigilance Branch (VB) has received a total of 37 local suspected ADR reports associated with strontium, out of which 30 described skin reactions. Eighteen reports were assessed as serious in nature by the reporting physicians. These serious reports include one report of dermatitis exfoliative, two reports of Stevens-Johnson syndrome (SJS) and three reports of toxic epidermal necrolysis (TEN), of which two were associated with fatal outcomes. These reports were received over a period of four years.

All the patients were elderly females (65 - 82 years old) with co-morbidities such as hypertension or hyperlipidaemia and were on concomitant medications (eg, anti-hypertensives, lipid-lowering agents, cyclooxygenase-2 inhibitor). Five of the patients were Chinese and one was a Malay. In some cases, strontium was identified as the only suspected drug due to its recent initiation to the patient's regular drug regimen. The time to onset ranged from nine to 34 days. Some of these cases presented with initial flu-like symptoms followed by the development of rash over the trunk and limbs.

Overseas reports

From 2005 to May 2011, a total of 1,220 global ADR reports associated with strontium ranelate were reported in the World Health Organisation (WHO) Vigibase*.

Of these reports, more than 30% involved the skin and subcutaneous tissues, with some describing serious conditions such as drug rash with eosinophilia, alopecia and angioedema. Other than the above reports from Singapore, a total of six other reports of SJS and three reports of TEN were reported by some European countries and Malaysia.

**WHO Vigibase is a global database of adverse reaction reports on medicinal products which are contributed by more than 80 pharmacovigilance centres worldwide, including Singapore.*

Regulatory actions taken to date

Serious skin reactions with strontium ranelate is not a new occurrence. In November 2007, the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) alerted on an increasing number of reports of 'drug rash with eosinophilia and systemic symptoms' (DRESS)** associated with the use of strontium.[2] The CHMP noted that symptoms of DRESS appeared within three to six weeks after the patients started to take strontium. It was also concerned that the link between strontium and DRESS was not recognised immediately, leading to a delay in stopping the causative agent. This in turn led to poor prognoses of the patients. Hence, the committee concluded that a warning on the risks of DRESS should be introduced in the medicine's prescribing information, stating that patients showing symptoms of DRESS should stop treatment and contact their doctor immediately.

The March 2008 issue of the HSA Adverse Drug Reaction News bulletin[3] similarly carried an article to alert prescribers of the risk of serious skin reactions with strontium. Consequently, the package insert (PI) of Protos® was revised to include DRESS and SJS in 2008. Following reports of TEN through post-market surveillance effort, the PI of Protos® was revised again in 2010 to include TEN as part of the "skin and subcutaneous tissue disorders" adverse reactions. HSA continues to work with the company to closely monitor reports of serious skin reactions related to strontium ranelate to ensure that the benefit-risk profile of the drug remains favourable.

*** DRESS is a rare but serious and life-threatening type of allergic reaction to a drug. The condition starts with a skin rash, accompanied by a fever, swollen glands, eosinophilia, adenopathy and systemic involvement which may include hepatic, renal and pulmonary impairment.*

HSA's advisory

In view that these serious skin reactions are associated with significant morbidity and mortality, healthcare professionals are advised to be mindful of the local cases of serious skin reactions associated with strontium ranelate when prescribing the drug for treatment of postmenopausal osteoporosis.

As early signs of rash and skin reactions may be indicative of a more serious reaction such as SJS and TEN, healthcare professionals are advised to educate their patients on the early recognition of allergic reactions and to seek medical attention promptly. In addition, patients who have stopped treatment due to hypersensitivity reactions should not re-start therapy with strontium.

HSA will continue to monitor the situation closely and update healthcare professionals on any significant new findings. In the meantime, healthcare professionals are strongly encouraged to report all suspected ADRs associated with strontium ranelate to the Vigilance Branch of HSA.

References

1. *Osteoporosis Int. 2009; 20 (1): 161-162*
2. *http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2009/11/WC500015595.pdf*
3. *HSA Adverse Drug Reaction News. March 2008, Vol 10 No. 1*

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All website references were last accessed on 1 Aug 2011.