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Adverse Drug Reaction News

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Bupivacaine (Marcain®) and reports of lack of efficacy

The Vigilance Branch of HSA has from September 2009 to March 2010, received a clustering of reports on the lack of efficacy associated with the use of bupivacaine preparations (Marcain® 0.5% and Marcain® Spinal 0.5% Heavy Injection, AstraZeneca, AZ) when used during spinal anaesthesia. This finding led to a series of follow-up investigations to determine the possible causes of failed spinal anaesthesia (FSA).

Marcain® Spinal 0.5% Heavy Injection and Marcain® 0.5% Injection have been registered in Singapore since April 1991 and July 2006 respectively and are indicated for the production of spinal anaesthesia. Marcain® 0.5% is indicated for lower limb surgery lasting 3 – 4 hours where muscle relaxation is needed; and Marcain® Spinal 0.5% Heavy Injection is indicated for abdominal surgery lasting 45 – 60 minutes and urological and lower limb surgery lasting 2 – 3 hours.

Local reports of lack of efficacy

Three reports of lack of efficacy with Marcain® Spinal 0.5% Heavy Injection were first reported to HSA in September 2009 by different anaesthetists from a tertiary hospital. All three reports were associated with a single batch of Marcain® Spinal 0.5% Heavy Injection.

From December 2009 to February 2010, six additional cases of a similar nature were reported. These involved two different batches of Marcain® Spinal 0.5% Heavy injection.

Laboratory investigations

The HSA's Pharmaceutical Laboratory conducted an analysis of the affected batch involved in the first three cases reported in September 2009. The test result indicated that the bupivacaine content in Marcain® Spinal 0.5% Heavy Injection was within specifications. Nonetheless, the remaining stocks of Marcain® Spinal 0.5% Heavy Injection in the affected batch at the hospital were returned to the company and replaced with another batch.

Following the additional reports in December 2009 and early 2010, HSA contacted hospital pharmacies from both the private and public institutions to ascertain if they had similar experiences. One tertiary hospital provided retrospective reports of 13 cases involving both Marcain® 0.5% and Marcain® Spinal 0.5% Heavy Injection. The hospital also provided ampoules of Marcain® 0.5% Injection from these two affected batches, which were assayed by HSA's Pharmaceutical Laboratory and found to be within specifications.

Additional tests were performed by AZ to confirm that these products complied with the registered specifications. The data submitted by AZ for quality assessment included the certificate of analysis of the finished products, stability data and investigation reports. Based on the available information, it was concluded that the analytical test results were within the registered product specifications and that the products were stable during the specified shelf-life.

Similar experience in other countries and possible causes of FSA

Global estimates on the incidence of FSA range from 0.5 - 17%.[1,2] HSA's further investigations also revealed that some other agencies had also encountered similar patterns of FSA in the past. In all of the reported cases, there was no single identifiable cause and the cases involved more than one batch of the products. The outcome of these investigations showed that the causes of FSA were multifactorial.

Based on available literature, the following factors may contribute towards the occurrence of FSA: abnormalities of the spine such as kyphosis, scoliosis, calcification of ligaments, consequences of osteoporosis; patient's resistance to a specific anaesthetic; lumbar interspace selection; drug dosage; failed lumbar puncture; positioning of the patient and inadequate intrathecal spread.[1,3,4]

Conclusion

Spinal anaesthesia is an effective technique commonly used for local anaesthesia. Concerns about the quality of the anaesthetics may arise when a clustering of FSA occur in a hospital within a short period of time for straightforward procedures.

Based on the analyses to date, HSA has assessed that the causes of FSA could be a combination of many factors. As part of its educational efforts, AZ has conducted talks to hospitals to provide more information on the challenges of spinal anaesthesia, increase the awareness of FSA and highlight the importance of reporting such cases if encountered in the future.

Although no new cases of FSA has been reported since March 2010, HSA will continue to monitor this situation and update healthcare professionals when new information arises.

References

1. *Br J Anaesth 2009, 102 (6): 739-48*
2. *Eur J Anaesthesiol 1992, 9:7-13*
3. *Regional Anesthesia 1991, 16:48-51*
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CONTENTS

Zoledronic acid (Aclasta®) and reports of renal impairment

HSA would like to bring to the attention of healthcare professionals, post-marketing reports of renal impairment and renal failure associated with the use of intravenous zoledronic acid.

Zoledronic acid (Aclasta®, Novartis (Singapore) Pte Ltd) is a bisphosphonate that works by inhibiting osteoclast-mediated bone resorption, thereby slowing the breakdown of bone to reduce the risk of fractures. It has been licensed locally for use since March 2006 as a once-yearly intravenous treatment for osteoporosis in post-menopausal women and in men at increased risk of fractures; and for the treatment of Paget's disease of the bone.

Post-marketing reports of renal impairment

As of 14 August 2009, 139 post-marketing reports of renal impairment following Aclasta® infusion have been received by Novartis worldwide. This corresponds to an estimated reporting rate of 18 cases per 100,000 patient years. Majority of these cases have been reported in patients with pre-existing medical conditions or risk factors (advanced age, renal impairment, and concurrent or preceding dehydration) or who had concurrent exposure to nephrotoxic agents (e.g. NSAIDs). Rare cases of renal failure requiring dialysis or with a fatal outcome have been reported in patients with pre-existing renal impairment and concomitant risk factors.

US Food and Drug Administration (FDA)

From April 2007 to February 2009, the FDA's Adverse Event Reporting System received 24 evaluable post-market reports of renal impairment and acute renal failure associated with the use of Reclast® (the equivalent of Aclasta® in US).[1] The median time-to-onset from the date of infusion until the event was 11 days. The median age of the patients was 75 years old (range 61 – 89 years) with osteoporosis being the most frequent indication for the use of Reclast®. Although confounding factors such as underlying medical conditions and concomitant medications were noted in some of the cases, there were others whereby a reasonably possible association with Aclasta® could not be ruled out.

Of these 24 reports of renal impairment and acute renal failure, transient increases in serum creatinine were documented in 13 (54%) of the patients following infusion of the drug. The median increase in serum creatinine was 4mg/dl. Fourteen (58%) patients had underlying medical conditions (e.g. diabetes mellitus, congestive heart failure or chronic kidney disease) or had concurrent exposure to nephrotoxic medications (e.g. NSAIDs) that may have contributed to their risk of developing renal impairment or acute renal failure.

Majority (54%) of the 24 cases of renal impairment and acute renal failure improved following hydration with intravenous fluid administration. In several cases, acute renal failure, dialysis, and death were reported in patients with pre-existing renal insufficiency.

The package insert (PI) of Reclast® in the US has been updated to include data on acute renal failure following these post-marketing reports of renal impairment and acute renal failure.

UK Medicines and Healthcare products Regulatory Agency (MHRA)

As of 5 March 2010, there have been six suspected reports of renal impairment or renal failure following administration of Aclasta® in the United Kingdom (UK).[2] Majority of these cases generally occurred after the first dose and in patients with pre-existing renal dysfunction or other risk factors such as advanced age, the use of concomitant nephrotoxic drugs, diuretic therapy or dehydration. Renal failure requiring dialysis or resulting in death occurred in some high-risk patients.

A letter was sent to healthcare professionals in March 2010 highlighting the updated UK PI for Aclasta®.

Local situation

To date, HSA has received two reports of renal-related adverse reactions following Aclasta® infusion. The first patient was a female (age not reported) who experienced acute renal failure with elevated serum creatinine. The second patient was a 60 year-old female who developed renal impairment nine months after receiving Aclasta® infusion. The patient was noted to be also on concomitant medications such as amlodipine, esomeprazole, calcitrol, paracetamol and sodium bicarbonate.

A Dear Healthcare Professional Letter[3,4] was issued on 1 April 2010 by Novartis (Singapore) Pte Ltd, highlighting these post-marketing reports of renal failure and renal impairment following Aclasta® infusion. The local PI for Aclasta® has been updated to include these adverse reactions.

Physicians are reminded to consider their patient's renal function and assess serum creatinine before treatment with Aclasta®. When prescribing Aclasta® to patients, physicians are encouraged to refer to the latest updated PI for Aclasta®, available on the HSA's website and to report all adverse drug reactions associated with the use of Aclasta® to the Vigilance Branch of HSA.

References

1. *FDA Drug Safety Newsletter Vol 2, No. 2, 2009. Zoledronic acid (marketed as Reclast): Renal impairment and acute renal failure. http://www.fda.gov/Drugs/DrugSafety/DrugSafetyNewsletter/ucm167883.htm*
2. *MHRA Drug Safety Update: Vol 3, Issue 9, April 2010. Intravenous zoledronic acid: adverse effects on renal function. http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON076501*
3. *HSA website. Dear Healthcare Professional Letters (DHCPL). http://www.hsa.gov.sg/DHCPL*
4. *MOH-Health Professionals Portal: http://www.hpp.moh.gov.sg*

Orlistat and post-marketing reports of severe liver injury

The HSA's Vigilance Branch would like to update healthcare professionals on the post-marketing reports of liver injuries associated with the use of orlistat. Orlistat is a potent inhibitor of gastrointestinal lipases, thereby reducing the ingested dietary fat absorption and total energy intake to produce weight loss.

Orlistat is registered in Singapore under the trade names of Alli® (GSK) and Xenical® (Roche). Xenical® has been registered locally since 1999 and is indicated for the treatment of obese patients with a body mass index (BMI) ≥ 30 kg/m^2, or overweight patients (BMI ≥ 28 kg/m^2) with associated risk factors, in conjunction with a mildly hypocaloric diet. Alli® has been licensed for use locally in 2010, with the same indication as Xenical, and it is to be used in adults aged 18 years and older, along with a reduced-calorie and low-fat diet.

Reviews performed by drug agencies to date

US

The US Food and Drug Administration (FDA) has completed its review of the reports of serious liver injuries associated with the use of Xenical® and Alli®.[1] The agency had identified a total of 13 reports of severe liver injury associated with the use of these orlistat-containing medicines: 12 foreign reports with Xenical® and one U.S. report with Alli®. Of these 13 cases, two patients died from liver failure while three patients required liver transplantation. The FDA reported that a causal relationship between severe liver injury and the use of orlistat has not been established. This causality link was difficult to establish as these reports of severe liver injury had occurred over a period of 10 years, during which an estimated 40 million people worldwide could have consumed orlistat. Some of the patients in the reported cases had also taken other medications or had other medical conditions that may have contributed to the development of severe liver injury.

The FDA has included information regarding the cases of severe liver injury to the labels of Xenical® and Alli®. This is to increase awareness among healthcare professionals on these post-marketing cases of severe liver injury associated with the use of orlistat and to educate patients using these medicines about the signs and symptoms of liver injury.

Europe

A Europe-wide review on the possible association between serious hepatic reactions and orlistat use was conducted in July 2009.[2] The data that was reviewed included non-clinical, clinical trial, post-marketing safety data provided by the product licence holders and suspected adverse reaction reports submitted to the UK Medicines and Healthcare products Regulatory Agency. The European review concluded that there was insufficient evidence to show that either Xenical® or Alli® were associated with more serious liver disorders other than those currently listed in the product information (such as hepatitis, cholelithiasis, increased transaminases) and no further regulatory action was recommended.

Singapore

In August 2009, the Vigilance Branch, HSA undertook a safety review of the cases of hepatic disorders associated with the use of Xenical® that were submitted to the FDA. It was found that over 50% of these drug-induced hepatic reports were confounded by the use of concurrent medicines (e.g. alcohol, paracetamol, statins) or underlying medical conditions such as obesity and gallstones.

Local cases

Since 2000, HSA has received two local reports of liver toxicities suspected to be associated with the use of orlistat. The first case was reported in 2000, which described a case of jaundice and fulminant liver failure with massive hepatocellular necrosis in a 62 year-old man.[3] However, the causality of liver failure was unclear as the patient was also taking paracetamol. A second case was reported in 2002, whereby the patient was reported to have elevated liver enzymes.

HSA's advisory

The local patient information leaflets and package inserts of both Xenical® and Alli® currently carry warnings on the possible risk of hepatic-related adverse effects associated with the use of these medicines.

In view of the potential for rare but severe liver injuries, it is recommended that healthcare professionals consider the benefits and risks associated with the use of orlistat before prescribing or recommending these medications to their patients. Healthcare professionals are advised to inform their patients to stop the use of orlistat and seek medical attention immediately if they experience symptoms that may be possibly associated with liver injury, such as fever, jaundice, or brown urine. Healthcare professionals are encouraged to report any adverse drug reactions that are suspected to be associated with the use of orlistat to the Vigilance Branch of HSA.

References

1. *FDA Drug Safety Communication http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm213038.htm*
2. *MHRA Drug Safety Update: Vol 3, Issue 7, February 2010 http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON071085*
3. *Med Sci Law 2002, 42:309-12*

Communication channels for drug safety information and updates

The timely communication of safety information on health products and the regulatory actions taken to mitigate their risks is an important element of pharmacovigilance in enhancing safe and effective use of health products in Singapore. The Vigilance Branch, HSA would like to update on the various communication channels that are used to reach out to our stakeholders, such as healthcare professionals (HCPs) and members of the public.

Types of safety information communicated

The Vigilance Branch initiates communication in situations whereby new developments or safety findings may potentially have an impact on the use of the health products. Such situations include:

- Withdrawal or suspension of a health product
- Major safety issues associated with the use of a health product
- Safety information which may have significant impact on clinical practice
- Interim safety updates and regulatory positions while evaluating emerging safety signals associated with a health product
- Adulteration of a health product

Types of communication channels

The Vigilance Branch employs several communication channels to disseminate safety information and HSA's regulatory decisions to various stakeholders. These include:

- Dear Healthcare Professional Letters (DHCPLs)
- HSA Interim Safety Updates
- Adverse Drug Reaction (ADR) News Bulletin
- Press Releases
- Package Insert Updates
- HSA/Ministry of Health–Health Professionals Portal (MOH-HPP) Website

1. Dear Healthcare Professional Letters

DHCPLs are issued by either HSA or the product licence holder of the health products and are addressed specifically to HCPs, such as doctors, pharmacists and dentists. DHCPLs are used to update and alert on important and major safety concerns, e.g. the suspension or withdrawal of a medicine. DHCPLs are usually sent to HCPs via email, fax and post. An SMS or email alert, sent via the MOH-HPP, is used on rare occasions when critical and important safety information needs to be disseminated to HCPs rapidly. HCPs are reminded to ensure that they are registered with MOH-HPP to receive these notifications. Copies of all DHCPLs are archived at the MOH-HPP website at *http://www.hpp.moh.gov.sg/*.

2. HSA interim safety updates

The Interim Safety Update is part of the Vigilance Branch's efforts to communicate interim safety findings or regulatory positions to HCPs promptly while the emerging safety information continues to be evaluated by HSA and other regulatory agencies. The safety information disseminated using this communication channel is usually sent via email to various healthcare professional groups, e.g. Chairmen of Medical Boards, CEOs of Healthcare Institutions, Pharmacy Managers, Singapore Medical Association, Pharmaceutical Society of Singapore and College of Family Physicians Singapore. Interim safety updates can be found on HSA's website under the Product Safety Alerts at: *http://www.hsa.gov.sg/pdt_safetyalerts*

3. HSA Adverse Drug Reaction News bulletin

The HSA ADR News bulletin is a 4-monthly publication produced by the Vigilance Branch and the Pharmacovigilance Advisory Committee. This bulletin is sent to all registered medical doctors, pharmacists and dentists. The purpose of the bulletin is to highlight recent important safety issues. Earlier issues of the ADR News bulletin are available on the HSA's website at: *www.hsa.gov.sg/adrbulletin*

4. Press releases

Important messages that have major impact on public health and safety will be released to the press so as to reach out to the general public. This is part of HSA's effort to communicate and share with the public on findings and recommendations regarding serious safety issues associated with health products available in Singapore so that they can take actions to safeguard their own health. The press releases are available on the HSA's website: *http://www.hsa.gov.sg/press_releases*

5. Package insert updates

The package insert contains detailed information about the safety profile of the health product. All safety-related updates resulting in amendments to the local package insert are available on HSA's website at: *http://www.hsa.gov.sg/label_amend*

6. HSA/MOH-HPP website

Product safety alerts, summary of DHCPLs, safety-related label amendments, safety information listing by product and product recalls are posted at the *Safety Information and Recalls* section of the HSA website:

http://www.hsa.gov.sg/safetyinfo_and_recalls

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HSA hosts Pharmacovigilance training for ASEAN countries

Photographer: James Chan

Overview

More than 40 drug regulators from nine ASEAN countries (Brunei, Cambodia, Indonesia, Laos, Malaysia, Philippines, Thailand, Vietnam and Singapore) attended the inaugural WHO-UMC-HSA Basic Pharmacovigilance (PV) Training conducted in Singapore from 31 May to 4 June 2010. The joint initiative by the World Health Organisation (WHO), WHO's Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (UMC) and Health Sciences Authority (HSA) marked the first tailored training on PV developed for ASEAN countries.

The training aimed to equip participants with the necessary skills to strengthen PV capabilities in ASEAN nations, especially for developing countries who are in their initial stages of establishing PV Centres. These objectives were well aligned with the WHO-UMC's continual drive to communicate the importance of drug safety and PV among countries.

Key topics covered

Participants familiarised themselves with theories and best practices on PV activities, such as management of adverse drug reaction (ADR) reports and communication of safety information. Unique to the region, topics such as safety monitoring of traditional medicines were included.

In addition, participants engaged in group discussions to perform causality assessments of ADR reports and brainstorm on ways to encourage ADR reporting. There was also a hands-on data-entry session using VigiFlow™, which is a Case Management System for Individual Case Safety Reports (ICSR) from WHO.

International and local panel of speakers

Renowned experts in the field of PV chaired the training sessions. Representatives comprised Dr Shanthi Pal, Acting Programme Manager, WHO; Mr Sten Olsson, Chief WHO Programme Officer, UMC; Ms Monica Plöen, Manager of safety support services, UMC, and Dr John McEwen, adjunct associate professor in Pharmacy, University of Canberra.

Local clinical specialists were also invited to share their knowledge and area of expertise. They include Prof Chng Hiok Hee, Senior Consultant in Rheumatology, Allergy and Immunology, Tan Tock Seng Hospital and Prof Chow Wan Cheng, Senior Consultant in Gastroenterology and Hepatology, Singapore General Hospital. In addition, pharmacovigilance specialists from HSA who presented at this event include Ms Chan Cheng Leng, Division Director of Vigilance, Compliance and Enforcement and Ms Belinda Tan, Senior Regulatory Specialist, Vigilance Branch.

Moving forward

Participants were pleased with the training, which had given them a head start and added confidence to further their work in PV. As countries mapped out their PV plans for the next year, many pledged their commitment to further increase the awareness of ADR reporting in their countries.

As shared by Dr John Lim, CEO of HSA, the next step forward would be for countries to apply the knowledge gained in the course to enhance PV capabilities in their countries. This will hopefully pave the way for deeper future collaborations in the area of PV among ASEAN countries to enhance drug safety in the region.

The editorial team would like to thank Ms Larissa Tan for her contribution to this article.

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■ Communication channels for drug safety information and updates ■

- Product safety alerts (sorted by the year):
  http://www.hsa.gov.sg/pdt_safetyalerts

- Summaries of DHCPLs issued by the HSA or product licence holders (in consultation with HSA):
  http://www.hsa.gov.sg/DHCPL
  The full versions of the DHCPLs are archived at the MOH-HPP website.
- Safety-related product label amendments:
  http://www.hsa.gov.sg/label_amend
- Safety Information listing by product:
  http://www.hsa.gov.sg/pdt_safetyinfo
- Product recalls:
  http://www.hsa.gov.sg/pdt_recall

The safety information on the HSA website is updated on a regular basis and HCPs are encouraged to refer to the website regularly for safety information on health products of interest.

Intravascular haemolysis associated with WinRho® SDF injection

HSA would like to bring to the attention of healthcare professionals the potential risk of intravascular haemolysis (IVH) and its complications associated with Rho (D) Immune Globulin (Human) (WinRho® SDF) when used to treat Immune Thrombocytopenia Purpura (ITP).

WinRho® SDF is the gamma globulin (IgG) fraction of human plasma containing antibodies to the Rho (D) antigen (D antigen). It is indicated for the prevention of Rh immunisation in Rho (D) negative women at risk of developing Rh antibodies; prevention of alloimmunisation in Rho (D) negative individuals transfused with Rho (D) positive red blood cells (RBCs) or blood components with Rho (D) positive RBCs and for the treatment of ITP. It has been registered for use locally since 2008 and is available in three strengths: 600IU, 1500IU and 5000IU.

Global post-marketing reports of intravascular haemolysis (IVH)

From March 1995 to March 2009, Cangene Corporation (the manufacturer of WinRho® SDF) reported a total of 180 serious post-marketing reports of suspected and/or confirmed cases of IVH associated with the use of WinRho® SDF worldwide. Of the 180 serious cases, 58 (32%) were considered definite IVH, 59 (33%) were probable IVH and 47 (26%) were possible IVH. Seventeen of the 58 definite IVH cases (29%) reported fatal outcomes, of which 13 patients were over the age of 65 years and 15 patients had a history of serious underlying co-morbid diseases that were considered to have induced or exacerbated pathological conditions leading to fatal outcomes.

A disproportionate number of IVH cases has also been reported in patients with ITP secondary to haematological malignancies such as leukaemia or lymphoma, or active viral infections with Hepatitis C virus (HCV) and Epstein-Barr virus (EBV).

IVH can lead to clinically compromising anaemia and multi-system organ failure including acute respiratory distress syndrome. Serious complications such as severe anaemia, acute renal insufficiency, renal failure and disseminated intravascular coagulation have also been reported. Fatal outcomes associated with IVH and its complications have occurred most frequently in patients of advanced age (> 65 years) with co-morbid conditions.

Local regulatory actions

The local package insert (PI) for WinRho® SDF has been updated on the risk of IVH in patients treated for ITP, including new contraindications and conditions for use of WinRho® SDF in the treatment of ITP.

The new contraindications include patients with evidence of autoimmune haemolytic anemia or systemic lupus erythematosus or anti-phospholipid antibody syndrome; who are elderly with co-morbidities predisposing to acute haemolytic reactions or its complications; who are IgA deficient or who have ITP secondary to conditions such as leukemia, lymphoma, or active viral infections with EBV or HCV.

New conditions for use include recommendations that patients treated with WinRho® SDF for ITP should be closely monitored for at least 8 hours after administration together with a dipstick urinalysis at baseline, 2, 4 and 8 hours after administration. Absence of signs and/or symptoms of IVH within 8 hours do not indicate IVH cannot occur subsequently.

A Dear Healthcare Professional Letter was issued by Pharmaforte Singapore Pte Ltd on 27 May 2010 to all purchasers of WinRho® SDF to inform them of the above-mentioned safety concerns as well as the updates made to the local PI. This letter can also be accessed via the HSA's website and the MOH Healthcare Professional Portal (HPP).[1,2]

To date, HSA has not received any local adverse reaction reports associated with WinRho® SDF. Physicians are advised to be vigilant for signs and symptoms of IVH, including back pain, shaking chills, fever, and discoloured urine or haematuria in patients being treated with WinRho® SDF and report any suspected cases to the Vigilance Branch of HSA.

References

1. *HSA website. Dear Healthcare Professional Letters (DHCPLs). http://www.hsa.gov.sg/DHCPL*
2. *MOH-Health Professionals Portal: http://www.hpp.moh.gov.sg*

New Medicinal Product Approvals on HSA Website

HSA is pleased to announce that information on newly approved medicinal products will be available at HSA's website at: *http://www.hsa.gov.sg/monthly_approval* from August 2010.

The list provides information on medicinal products that are approved every month beginning from January 2010. This includes approvals for innovator products, new combinations, dosage forms or new usage of an innovator product. It also includes new indications that have been approved for existing medicinal products.

This is one of the new initiatives that HSA has embarked to share the latest medicinal product approvals with healthcare professionals in a timely manner. Should you have any feedback on this new e-service, please contact *Ms Wendy Goh* at *Tel: 6866 3417* or *email: Wendy_Goh@hsa.gov.sg*.

Package insert amendments reflecting safety issues

HSA has approved the following package insert changes due to safety updates from December 2009 to April 2010. Please note that due to space constraints, the list published is not exhaustive and you are encouraged to refer to the following website for the complete listing with details: **http://www.hsa.gov.sg/label_amend**. Please also note that there might be some lag time in the availability of the package insert which reflects the latest change(s).

1. Alfuzosin (Xatral® & Xatral SR®, sanofi-aventis) Contraindication: Ritonavir. Interactions: Risk of increased plasma alfuzosin concentration & undesirable effects when combined with ritonavir, ketoconazole, itraconazole, clarithromycin or erythromycin. Not advisable to combine anti-hypertensive alpha-receptor blockers, anti-hypertensives, nitrates, nitrites & related drugs due to enhanced hypotensive effect & risk of severe postural hypotension. Risk of postural hypotension, esp. in elderly subjects, when phosphodiesterase type 5 inhibitors (sildenafil, tadalafil, vardenafil) are combined. New ADRs: Lightheadedness, dizzy spells, angina pectoris in patients with a history of coronary artery disease, nasal congestion, hepatocellular injury, cholestatic hepatitis, priapism.

2. Aprepitant (Emend®, MSD) Interaction: Moderate CYP3A4 inhibitors (e.g. diltiazem) result in 2-fold increase in plasma concentrations of aprepitant. New ADRs: Palpitations, somnolence, malaise.

3. Betamethasone, gentamicin (Diprogenta® cream, Schering-Plough) Special warning: Cross-allergenicity among aminoglycosides. New ADRs: Hypersensitivity & skin discoloration.

4. Carbamazepine (Tegretol®, Novartis) Special warning: May trigger hypersensitivity reactions (HSR), including multi-organ HSR, which can affect skin, liver (including intra-hepatic bile ducts), haematopoietic organs & lymphatic system or other organs, individually or together in a systemic reaction. Interaction: May lower plasma level, diminish or abolish activity of buprenorphine, mianserin, sertraline. New ADR: Vanishing bile duct syndrome (destruction & disappearance of intra-hepatic bile ducts).

5. Celecoxib (Celebrex®, Pfizer) New ADRs reported post-market: Pulmonary embolism, chest pain.

6. Clomipramine (Anafranil® & Anafranil® SR, Novartis) Special warning: Increased risk of suicidal thinking & behaviour in short-term studies in children, adolescents & young adults <25 yo with depressive disorders & other psychiatric disorders. Interaction: Co-administration with terbinafine, a strong inhibitor of CYP2D6, may result in increased exposure & accumulation of clomipramine & its N-demethylated metabolite.

7. Doripenem (Doribax® powder for injection, J&J) Special warning: Doripenem reduced serum valproic acid concentrations to sub-therapeutic levels in healthy subjects. Interaction: Monitor serum valproic acid concentrations in the blood if administered concomitantly with valproic acid or sodium valproate, & consider alternative therapies. New ADRs reported post-market: Thrombocytopenia, TEN, SJS.

8. Ertapenem (Invanz®, MSD) & Imipenem, cilastatin (Tienam® for injection, MSD) Precautions: Co-administration of ertapenem & valproic acid or divalproex sodium results in reduction of valproic acid concentrations to sub-therapeutic range thereby increasing the risk of breakthrough seizures. Increasing the dose of valproic acid or divalproex sodium may not be sufficient to overcome this interaction. Antibacterials other than carbapenems should be considered to treat infections in patients whose seizures are well controlled on valproic acid or divalproex sodium. If administration of Invanz® or Tienam® is necessary, supplemental anticonvulsant therapy should be considered.

9. Glimepiride, rosiglitazone (Avandaryl®, GSK) & Metformin, rosiglitazone (Avandamet®, GSK) & Rosiglitazone (Avandia®, GSK) Warnings & precautions: Studies showed rosiglitazone to be associated with increased risk of myocardial ischaemic events in placebo-controlled but not active-controlled trials. Long-term studies show increased incidence of bone fracture in patients, esp. female patients, taking rosiglitazone. Majority of fractures occurred in upper & distal lower limbs. Increased incidence noted after 1st year of treatment & persisted during long term treatment. ADRs: Increased incidence of heart failure when rosiglitazone (at both 4 mg & 8 mg) was added to treatment regimens that included sulphonylurea (SU), metformin or insulin. Increased incidence of bone fractures when rosiglitazone was added to treatment regimens that included metformin or SU. Additional ADRs for **Avandamet®**: Increased incidence of oedema, anaemia, hypercholesterolaemia, weight gain & hypoglycaemia.

10. Human Papillomavirus vaccine (Cervarix®, GSK) New ADRs reported post-market: Anaphylactic & anaphylactoid reactions, angioedema, syncope or vasovagal responses to injection, sometimes accompanied by tonic-clonic movements.

11. Indomethacin (Indocin® IV, Merck) New ADRs: Renal failure, thrombocytopenia.

12. Isotretinoin (Roaccutane®, Roche) Precautions: Severe skin reactions e.g. EM, SJS, & TEN reported. May be serious, life-threatening resulting in hospitalization or disability, and may be fatal. Monitor patients closely for severe skin reactions & discontinue therapy if warranted.

13. Itraconazole (Sporanox®, J & J) New ADRs reported post-market: Pancreatitis, pyrexia.

14. Laropiprant, niacin ER (Tredaptive®, MSD) Precautions: Incidence of myopathy higher than expected in Chinese patients. Use cautiously when treating Chinese patients with Tredaptive® co-administered with simvastatin or ezetimibe/simvastatin (esp. simvastatin doses of 40 mg or higher). Risk of myopathy with statins is dose-related, and concomitant use with simvastatin 80 mg or ezetimibe/simvastatin 10/80 mg is not recommended in Chinese patients.

15. Levodopa, carbidopa, entacapone (Stalevo®, Novartis) Special warnings: Administer with caution to patients with ischaemic heart disease, severe cardiovascular or pulmonary disease, bronchial asthma, renal, or endocrine disease, or history of peptic ulcer disease or convulsions. Prolonged or persistent diarrhoea may be a sign of colitis. Discontinue therapy in prolonged or persistent diarrhoea. New ADRs: Ischaemic heart disease events e.g. angina pectoris, myocardial infarction, angioedema.

16. Methotrexate (Methotrexate®, Wyeth) Special warnings: Fatal toxicities related to inadvertent daily rather than weekly dosing reported, esp. in elderly patients. Methotrexate has caused reactivation of hepatitis B infection or worsening of hepatitis C infections, sometimes resulting in death. Cases of hepatitis B reactivation have occurred after discontinuation of methotrexate. Perform clinical & laboratory evaluation to evaluate pre-existing liver disease in patients with prior hepatitis B or C infections. Precautions: Leukoencephalopathy reported in patients who received oral methotrexate. Cases of severe neurological ADRs ranging from headache to paralysis, coma & stroke like episodes reported mostly in juveniles & adolescents given methotrexate in combination with cytarabine. Monitor patients undergoing methotrexate therapy closely to detect toxic effects promptly. Interactions: Vitamin preparations containing folic acid or its derivatives may decrease responses to systemically administered methotrexate and increase methotrexate toxicity. New ADRs: Reactivation of hepatitis B infection, worsening of hepatitis C infection, leukoencephalopathy (oral methotrexate).

17. Phenytoin (Dilantin®, Pfizer) Special warning: Potential for increased risk of suicidal thoughts or behaviours.

18. Piroxicam (Apo-piroxicam®, Apotex; Brexin®, IDS) Contraindications: Patients with active peptic ulcer, inflammatory GI disorder or GI bleeding, gastritis, dyspepsia, severe hepatic or renal diseases, moderate or severe heart failure, severe hypertension, severe blood diseases or haemorrhagic diathesis; Patients on concomitant NSAIDs or anticoagulants; Patients with history of previous serious allergic drug reaction e.g. SJS, TEN & EM; Patients hypersensitive to piroxicam, or had previous skin reaction to piroxicam, other NSAIDs. Should not be given to patients in whom ASA or other NSAIDs have induced asthma, rhinitis, nasal polyposis, angioedema, or urticaria. Warnings: Increased risk of serious GI event (including bleeding, ulceration, & perforation of the stomach, small intestine or large intestine, which can be fatal) in both long & short exposure. Studies suggest piroxicam may be associated with high risk of serious GI toxicity, relative to other NSAIDs. Risk for developing serious GI complications increase with age & in patients taking concomitant oral corticosteroids, SSRIs or anti-platelet agents. Consider combination therapy with gastro-protective agents for patients at high risk of GI complications. Serious skin reactions, some fatal, including exfoliative dermatitis, SJS & TEN, reported very rarely. Piroxicam may be associated with higher risk of serious skin reactions than other non-oxicam NSAIDs. Re-evaluate clinical benefit & tolerability periodically & discontinue treatment immediately at first appearance of skin reactions or GI events. Use of NSAIDs (esp.at high doses & for prolonged treatments) may be associated with increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction or stroke. Piroxicam can lead to onset of new hypertension or worsening of pre-existing hypertension. Evaluate before starting prolonged treatment in patients at risk of cerebro-vascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking). Not to be used perioperatively in patients who have recently undergone coronary artery bypass graft (CABG) surgery & revascularisation procedures. Use with caution in patients with impaired hepatic function. Due to interaction with arachidonic acid metabolism, piroxicam may induce bronchospasm, & possibly shock & other allergic reactions in asthmatic or predisposed patients. Ocular changes observed during NSAIDs therapy. Not recommended for use in children <16 yo. Interactions: Patients taking concomitant oral corticosteroids, SSRIs, anticoagulants e.g. warfarin or anti-platelet agents e.g. low-dose ASA are at an increased risk of serious GI complications. NSAIDs may reduce efficacy of diuretics & other anti-hypertensive drugs. Hyperkalaemia can occur in the case of concomitant administration with potassium-containing drugs, or diuretics that cause potassium retention. Concomitant administration of lithium & NSAIDs causes increase in plasma lithium levels. Monitor closely patients receiving piroxicam concurrently with other highly protein bound drugs for dosage adjustments. May reduce efficacy of IUDs. Concomitant use of NSAIDs & quinolone drugs not recommended. New ADRs: Reversible increase in blood urea nitrogen during prolonged treatment with piroxicam, which usually returns to baseline upon discontinuation of therapy. Bladder disorder, shock & warning symptoms, hair loss & impairment of nail growth. Rare cases of pancreatitis reported.

19. Rivastigmine (Exelon®, Novartis) Special warnings: May exacerbate extrapyramidal symptoms; worsening of Parkinsonian symptoms, esp. tremor; worsening of Parkinson's disease. New ADRs reported post-market: Hypertension, application site hypersensitivity, pruritus, rash, erythema, urticaria, blister, allergic dermatitis, tachycardia, atrioventricular block, atrial fibrillation, pancreatitis, fall, seizure. Cerebrovascular accident, erythema, urticaria, blister, allergic dermatitis observed.

20. Simvastatin (Zocor®, MSD) Precautions: Predisposing factors for myopathy: ≥65 years old, female gender, uncontrolled hypothyroidism & renal impairment. Patients on diltiazem/amlodipine treated concomitantly with simvastatin 80mg had increased risk of myopathy. Not recommended to exceed 40mg daily in patients receiving concomitant medication with diltiazem unless clinical benefit outweighs increased risk of myopathy. Periodic CK determinations recommended for patients titrating to 80mg dose though no assurance that this will prevent myopathy. Patients ≥65 yo had increased risk of myopathy compared to patients <65 yo when treated with simvastatin 80mg/day.

21. Strontium ranelate (Protos®, Servier) Special warning: Patients who have stopped treatment due to hypersensitivity reactions or other serious allergic reactions should not re-start therapy. New ADRs: Increased serum transaminase & pyrexia (in association with hypersensitivity skin reactions), TEN, peripheral oedema, confusional state, bronchial hyperreactivity, increased blood creatinine kinase. Not recommended for use in children & adolescents <18yo.

22. Telbivudine (Sebivo®, Novartis) Special warning: Isolated cases of rhabdomyolysis reported post-market.

23. Tenecteplase (Metalyse®, Boehringer Ingelheim) Contraindication: Hypersensitivity to gentamicin (a trace residue from manufacturing process). Special precautions: Reperfusion arrhythmias may lead to cardiac arrest which can be life threatening & may require use of conventional antiarrhythmic therapies. Anaphylactoid reactions are rare & can be caused by hypersensitivity to tenecteplase, gentamicin or excipient(s). Discontinue if anaphylactoid reaction occurs.

24. Tigecycline (Tygacil® injection, Wyeth) Special warnings: Anaphylaxis/anaphylactoid reactions reported & may be life-threatening. Isolated cases of significant hepatic dysfunction & hepatic failure reported. New ADR: Hepatic cholestasis.

25. Vigabatrin (Sabril®, sanofi-aventis) Special warnings: Monitor patients closely for signs of suicidal ideation or behaviour. Advise patients & care-givers to seek medical advice when such signs appear.

Summary on the findings of porcine circovirus DNA fragments in human rotavirus vaccines

This review provides a summary of the recent findings regarding the presence of DNA fragments of porcine circovirus type 1 (PCV-1) in Rotarix® and DNA fragments of porcine circovirus type 1 and 2 (PCV-1 and PCV-2) in RotaTeq® and the actions taken by HSA to date.

Rotarix® (GlaxoSmithKline, GSK) and RotaTeq® (Merck Sharp and Dohme, MSD) are the two rotavirus vaccines licensed in Singapore since October 2005 and June 2007 respectively for the vaccination of infants six weeks and older against gastroenteritis due to rotavirus infection.

Summary of updates on Rotarix® and RotaTeq®

a) Rotarix®

Using an advanced technology, researchers from the University of California, San Francisco (UCSF) had identified DNA fragments of PCV-1 in Rotarix®.[1] Further investigations conducted by GSK and the US Food and Drug Administration (FDA) confirmed the presence of PCV-1 DNA fragments in Rotarix® and its starting materials.

Ongoing investigations showed that the PCV-1 DNA fragments found in the final vaccine are unlikely to cause infection in human cells when used at recommended doses. Current available data also suggests that there were no cases of PCV-1 infection in infants who had received Rotarix® in clinical trials.

b) RotaTeq®

While initial tests in RotaTeq® conducted by the researchers at UCSF and FDA were negative for PCV DNA fragments, additional testing conducted by MSD detected very low levels of PCV-1 and PCV-2 DNA fragments in vaccine intermediates and PCV DNA in RotaTeq®. Additional tests to further understand these results and their significance are in progress.

Information on PCV-1 and PCV-2

PCV-1 and PCV-2 are not derived from the pig mammal. PCV-1 is found in pigs but it has not been linked to any animal disease. PCV-2 is a variant of PCV-1 and has been known to cause illness in pigs. There is however no evidence so far that PCV-1 and PCV-2 can infect humans and both are not known to cause illness in humans.

Recommendations of the Expert Committee on Immunisation (ECI)

HSA convened a meeting with the ECI, MOH in May 2010 to discuss the benefit-risk profile of the two licensed rotavirus vaccines based on these recent findings. The meeting took into consideration the safety profile of both rotavirus vaccines when administered to millions of vaccine recipients and current information on the infectivity of PCV-1 and PCV-2. In view that rotavirus infection is a common cause of viral-induced gastroenteritis in children locally, the ECI has recommended that both rotavirus vaccines should remain in use as the benefits of vaccination continue to outweigh the theoretical risk of PCV infectivity.

US FDA's regulatory decisions and actions

In March 2010, FDA provided an early communication on the finding of PCV-1 DNA fragments in Rotarix® and recommended the temporary suspension of the use of Rotarix® while investigations were ongoing. In May 2010, FDA updated on the findings of DNA fragments of PCV-1 and PCV-2 in Rotateq®. Following its advisory committee meeting, the FDA recommended that it was appropriate for healthcare professionals to resume the use of Rotarix® and to continue the use of RotaTeq® based on current data reviewed. [2]

HSA's assessment and recommendations

Based on available scientific and clinical data together with the expert opinions of the ECI, HSA has assessed that the benefits of the rotavirus vaccination currently outweigh the theoretical risk of PCV infectivity.

A Dear Healthcare Professional Letter[3,4] was sent on 18 May 2010 to inform healthcare professionals that they could consider the use of Rotarix® in patients who have previously deferred vaccination. Patients who have started or have been switched to the RotaTeq® vaccination schedule may wish to complete their course of vaccination. Parents should be made aware of the presence of the PCV DNA in these vaccines so that they can make an informed decision before deciding on vaccination. It is to be noted that rotavirus vaccination is optional and is not included in the national Childhood Immunisation Programme.

HSA also issued a press release on the use of rotavirus vaccines in Singapore on 19 May 2010.[5] The advisory to public was that infants who were currently on a rotavirus vaccination schedule may wish to complete the course of vaccination as advised by their doctors. Parents with concerns could seek more information from their doctors prior to the vaccination of their infants.

To date, the Vigilance Branch has not received any local adverse event reports associated with rotavirus vaccines which appear to be related to this issue. HSA will continue to monitor the situation and will update healthcare professionals as appropriate.

References

1. *J Virol 2010, 84(12):6033-40*
2. *US FDA Update on recommendations for the use of rotavirus vaccine. May 14, 2010 http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm212140.htm*
3. *HSA website. Dear Healthcare Professional Letters (DHCPL). http://www.hsa.gov.sg/DHCPL*
4. *MOH-Health Professionals Portal: http://www.hpp.moh.gov.sg*
5. *HSA Press releases: http://www.hsa.gov.sg/press_releases*

Enquiries, comments and suggestions to:
Vigilance Branch
Health Products Regulation Group
Health Sciences Authority

11 Biopolis Way, #11-03,
Helios, Singapore 138667

Tel: (65) 6866 3538
Fax: (65) 6478 9069

Website: http://www.hsa.gov.sg
Email: HSA_productsafety@hsa.gov.sg

All website references were last accessed on 15 July 2010.