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Adverse Drug Reaction News

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Vertical transmission of hepatitis B despite immunoprophylaxis

HSA would like to update healthcare professionals on several cases of vertical transmission of hepatitis B (HB) despite immunoprophylaxis with both HB immunoglobulin (HBIG) and HB vaccine. The infants were born to HB carrier mothers and had received a single dose of HBIG at birth and completed a three-dose regimen of HB vaccine. As of end-September 2012, HSA has received a total of 21 reports of HB immunoprophylaxis failure.

In Singapore, two brands of monovalent HB vaccine are currently marketed (Engerix-B®, GlaxoSmithKline and HBvaxPRO®, Merck Sharp & Dohme). Hexavalent vaccines such as Infanrix Hexa®, which contains HB antigen, may be used for second or third dose of HB vaccination. Three brands of HBIG are available in the market, namely HyperHEP B® (previously named BayHEP B®) from Skyquest, Anti-Hepatitis B Immunoglobulin Grifols® and Niuliva® Solution, both from Grifols Asia Pacific.

Review of the case reports

The 21 case reports of HB immunoprophylaxis failure were submitted to HSA in 2012 following screening for HB status (conducted in 2011 or 2012) or captured via a retrospective review. The screening was possibly triggered by MOH's 2011 advisory to screen infants born to HB carrier mothers after they had completed their primary course of HB vaccination, as well as an ongoing research study at a tertiary hospital.

Of these reports, six cases involving children born before 2009 were excluded from HSA's causality assessment due to a lack of critical information such as the brand of the implicated HBIG and HB vaccine and/or whether the children were infected within the first two years of life. The remaining 15 cases all involved the use of HyperHEP B® and Engerix-B®. Details of the HB vaccination schedule and brand of HB vaccine implicated are provided in Table 1.

Table 1. Details of the vaccination schedule and the brand of HB vaccine implicated in cases of hepatitis B vertical transmission despite immunoprophylaxis

Year of birth	Number of cases	Vaccination schedule for HB vaccine (Engerix-B®)		
		At birth, Month 1 Month 6,	Day 3, Month 1, Month 6	Day 3 Month 1 Month 18
1997, 2003, 2004, 2005	1 per year	Excluded from causality assessment due to lack of critical information		
2007	2			
2009	6	5 [a]	1 [b]	–
2010	8	6	1	1
2011	1	–	1	–
Total	**21**	**11**	**3**	**1**

[a] Infanrix Hexa® was given as the third dose for 1 infant
[b] HBvaxPRO® was given as the second dose

Of the 15 cases that were assessed, only one infant tested negative for HB virus (HBV) DNA viral load, HBe antigen (HBeAg) and HB surface antigen (HBsAg) but positive for antibodies against HBe and HBs (anti-HBe and anti-HBs) at two years of age, indicating transient infection.

As shown in Table 1, there were slight differences in the HB vaccination schedule among the 15 infants included in the assessment. With regard to the use of different brands of HB vaccine, monovalent HB vaccines are considered immunologically comparable based on studies conducted. It is recommended for infants born to HB carrier mothers to use monovalent HB vaccines for all three doses for optimal protection due to lack of data on the interchangeability between hexavalent and monovalent HB vaccines for these infants. Although two infants did not receive monovalent HB vaccine as the third dose or as scheduled, the first two doses of the vaccine should confer some protection. In addition to the HB vaccine, all the 15 infants received HBIG at birth for immunoprophylaxis against HB.

For these cases, the rates of immunoprophylaxis failure were estimated using data from the National Immunisation Registry (NIR) on the number of infants receiving HBIG at birth. The failure rates of 0.90%, 1.35% and 0.16% in 2009, 2010 and 2011, respectively, were found to be within the expected incidences reported in literature.[1]

Factors associated with immunoprophylaxis failure

HB vaccination and one dose of HBIG, administered within 24 hours after birth, are 85–95% effective in preventing both HBV infection and the chronic carrier state, whereas HB vaccine, administered alone within 24 hours after birth, is 70–95% effective in preventing perinatal HBV infection.[1] The use of HBIG alone reduced HBV occurrence by an average of 50%, dependent on the maternal HBeAg status.[2]

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Appropriate route for the administration of bortezomib (Velcade®)

HSA would like to remind healthcare professionals that the correct procedure for administering bortezomib (Velcade®, Janssen) is via the intravenous route and to recommend additional measures to reduce the risk of incorrect administration.

Bortezomib is indicated in the treatment of multiple myeloma and mantle cell lymphoma. With the apparent increase in incidence of CNS myeloma, the addition of intrathecal chemotherapy to established bortezomib-based protocols may become a more common practice.[1]

Cases of death associated with inadvertent intrathecal administration of Velcade®

The European Medicines Agency had recently released information regarding three fatalities resulting from bortezomib being accidentally administered intrathecally instead of by the intended intravenous route. In all these fatal cases, intrathecal chemotherapy was scheduled at the same time as bortezomib intravenous administration.[2] In response, a Dear Healthcare Professional Letter, containing specific precautionary measures, was sent out early this year by Janssen to remind healthcare professionals that Velcade® should be given intravenously.

Recommended precautionary measures

In order to reduce administration route errors, the following specific precautionary measures should be considered:

- When possible, use different connectors for medicinal products to be administered via the intrathecal as compared to those administered via the intravenous route.
- When possible, administer intrathecal and parenteral chemotherapy at different times.
- All intrathecal drugs should be packaged separately and clearly labelled both on the syringe and outer container, "For Intrathecal Use". Bortezomib should be clearly labelled both on the syringe and outer container, "For Intravenous or Subcutaneous Use Only; Fatal if Given by Other Routes."
- Appropriate procedures should be put in place to enforce double checking of syringe labels before administration.
- Specifically designated containers should be used for intrathecal drugs, both for transportation from the pharmacy and for storage in the administration area.
- When possible, intrathecal drugs should be delivered to the administration area separately from drugs to be given by other routes.
- Intravenous and intrathecal injections should be prescribed, dispensed, prepared, administered and transported only by trained and authorised healthcare professionals.
- Train and inform healthcare professionals involved in administration and/or management of oncology chemotherapy on dangers of intrathecal administration of Velcade® and the above risk minimisation measures.

Healthcare professionals are advised to take into consideration the above safety precautions when administering Velcade® and are encouraged to report any serious adverse events suspected to be associated with the use of Velcade® to the Vigilance Branch of HSA.

References

1 *J Clin Oncol 2012; 30(27):3427-3428*
2 *http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2012/01/WC500120701.pdf*

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Vertical transmission of hepatitis B despite immunoprophylaxis

In several prospective trials, immunoprophylaxis failure ranging from 8% to 32% has been reported among HBeAg positive mothers with high HBV DNA levels.[3] Risk factors analysis suggested that maternal HBeAg positivity and detectable HBV DNA were the most important factors associated with mother-to-child transmission despite immunoprophylaxis.[3,4] This may be attributed to intrauterine transmission, which is estimated to occur in <5% infants.[4] Further studies indicate that a serum HBV DNA level ≥8 $\log_{10}$ copies/mL was considered an important factor leading to immunoprophylaxis failure. In addition, HBV DNA in cord blood was a significant independent risk factor for such failure.[3]

While some studies have identified mutations in surface HBsAg, such as those located at the "a" determinant domain to which HBIG/HB vaccine elicits antibodies to bind, as possible causes of immunoprophylaxis failure,[5] others suggest that the mutations account for only a marginal role.[6,7] In contrast, other obstetrical and perinatal factors such as the mode of delivery,[8] premature birth, low birth weight and birth length[3] have not been found to be conclusively linked to immunoprophylaxis failure.

Discussion

a) Possible causes of the increase in the number of reports

A more in-depth analysis of the immunoprophylaxis failure cases to determine their possible cause is difficult due to the lack of information on the serologic profile of the mothers at birth. In addition, the increase in the number of reports could also be due to heightened awareness among healthcare professionals following MOH's advisory in 2011 to screen infants born to HB carrier mothers for seroconversion three months after completing the primary course of HB vaccination. More cases of vertical transmission of HB may have surfaced through proactive screening.

b) Assessment of product quality

A total of nine batches of Engerix-B® and four batches of HyperHEP B® were implicated in the cases of vertical transmission. A review of the certificates of analysis for the implicated batches found them to conform to the current registered product specifications before lot release. Registered changes since 2009 to the chemistry, manufacturing and controls (CMC) of Engerix-B® and HyperHEP B® have been examined to reconfirm that the changes have no impact on product quality and safety.

Conclusion

It is difficult to identify the root cause of vertical transmission of HB in these cases in view of incomplete data and the multi-factorial nature of immunoprophylaxis failure. Literature reports of failures of within 5% to 32% have been reported due to multiple reasons.

As HSA continues to monitor the issue, healthcare professionals are strongly encouraged to report all cases of HBV infection despite immunoprophylaxis to the Vigilance Branch of HSA.

References

1 *http://www.who.int/csr/disease/hepatitis/whocdscsrlyo20022/en/index4.html*
2 *BMJ 2006; 332(7537):328-336*
3 *J Viral Hepatitis 2012; 19:e18-e25*
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* *The editorial team would like to thank Dr Thoon Koh Cheng, Head and Consultant (Infectious Diseases Services, Department of Paediatrics) and Dr Liew Woei Kang, Visiting Consultant (Rheumatology & Immunology, Paediatric Subspecialties) from KKH for their clinical inputs in the above article.*

Look out for the inaugural publication of the Medical Device Alert circular bringing you updates on recent Field Safety Corrective Actions (FSCA).

Safety updates on the risk of QT prolongation and cardiac arrhythmia, including Torsades de Pointes with intravenous ondansetron

HSA would like to update healthcare professionals on the new dose restriction for intravenous (IV) ondansetron. The new maximum single IV dose for the management of chemotherapy-induced nausea and vomiting (CINV) in adults is 16mg, infused over at least 15 minutes. This new restriction is in response to concerns raised by the results of a new study demonstrating a dose-dependent prolongation of the QT interval with IV ondansetron, which could predispose patients to develop Torsades de Pointes.

Background

Ondansetron is a 5-HT_3 receptor antagonist, indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy as well as for the prevention and treatment of post-operative nausea and vomiting in adults and children 2 years and older. Three ondansetron-containing injections (2mg/mL) are registered in Singapore, namely Zofran® (GlaxoSmithKline), Ondansetron Hexal (Novartis) and Setronax (Drug Houses of Australia) since 1990, 2007 and 2009, respectively.

In 2011, HSA strengthened the local package inserts (PIs) to alert healthcare professionals to the risk of QT interval prolongation and cardiac arrhythmia, including Torsade de Pointes which were observed from postmarketing surveillance.

Further information on the degree of QT interval prolongation associated with ondansetron was reported in a recently completed study conducted by GSK. This was a double-blind, randomised, placebo- and active- (moxifloxacin 400mg) controlled crossover study to evaluate the effect of ondansetron on the QT interval in 58 healthy adult men and women. Ondansetron doses included 8mg and 32mg infused intravenously over 15 minutes. The preliminary results demonstrated that at the highest tested dose of 32mg IV, the maximum mean difference in QT duration corrected for heart rate by the Fridericia's formula (QTcF) compared to placebo after baseline-correction was 19.6ms (upper limit of 90% CI: 21.5). This degree of prolongation showed that the dose of 32mg IV could be clinically significant in certain individuals at risk for ventricular proarrhythmia. After exposure to a lower tested dose of 8mg IV, the maximum mean difference in QTcF compared to placebo after baseline-correction was 5.8ms (upper limit of 90% CI: 7.8), which is generally considered to be associated with a lower risk of proarrhythmia. Based on exposure-response modelling, it was predicted that an IV dosing regimen of 16mg, given over 15 minutes would result in a QTcF prolongation of 9.1ms (upper 95% CI: 11.2), an extent that is not expected to be associated with an increased risk of cardiac arrhythmias. No clinically important changes were observed in the measured electrocardiographic PR intervals, QRS duration or the heart rate across all treatment groups.

Actions by other regulatory agencies

The UK Medicine and Healthcare products Regulatory Agency (MHRA) has also issued a new dose restriction for IV ondansetron, with a maximum single IV dose of 16mg for the management of CINV in adults.[1] The US Food and Drug Administration (FDA) has informed healthcare professionals and the public about the risk of QT interval prolongation with the use of a single IV dose of 32mg ondansetron and recommended that a single IV dose of ondansetron should not exceed 16mg.[2]

Local situation

To date, HSA has not received any local adverse reaction report on QT prolongation with the use of ondansetron. HSA will continue to work with the companies to update the local PIs for Zofran®, Ondansetron Hexal® and Setronax® injections to reflect the new dosing and warning recommendations.

HSA's advisory

Healthcare professionals should be aware of the following dose restrictions and precautions to minimise the risk of QT prolongation and cardiac arrhythmia, including Torsade de Pointes with the use of IV ondansetron:

1. A single dose of IV ondansetron given for the management of CINV in adults must not exceed 16mg (infused over at least 15 minutes)
2. Ondansetron should be avoided in patients with congenital long QT syndrome
3. Caution must be used if administering ondansetron to patients with risk factors for QT interval prolongation or cardiac arrhythmias. These include:
   - electrolyte abnormalities
   - congestive heart failure
   - bradyarrhythmias
   - use of other medicines that prolong the QT interval (including cytotoxic drugs), or may lead to electrolyte abnormalities
   - use of medicines which lower the heart rate
4. Hypokalaemia and hypomagnesaemia should be corrected prior to ondansetron administration

There are no changes to the recommended dosing for the following indications or patient populations:

- IV dosing for the prevention and treatment of post-operative nausea and vomiting in adult patients
- IV dosing for any indication in the paediatric population
- dosing for CINV using oral ondansetron formulations in adults and paediatric patients

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

References

1 *http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON178189*

2 *http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm310219.htm*

■ ***Look out for the inaugural publication of the Medical Device Alert circular bringing you updates on recent Field Safety Corrective Actions (FSCA).*** ■

New look for the Health Products Regulation Group (HPRG) home page

HSA is pleased to announce that we have embarked on a revamp of the HSA website to improve users' surfing experience and provide faster access to safety alerts and other regulatory information. The revamp will be conducted in phases, starting with the Health Products Regulation Group (HPRG) home page. Healthcare professionals or members of the public can get the latest safety updates, information on reclassified medicines or search for medicinal products registered in Singapore from this revamped home page.

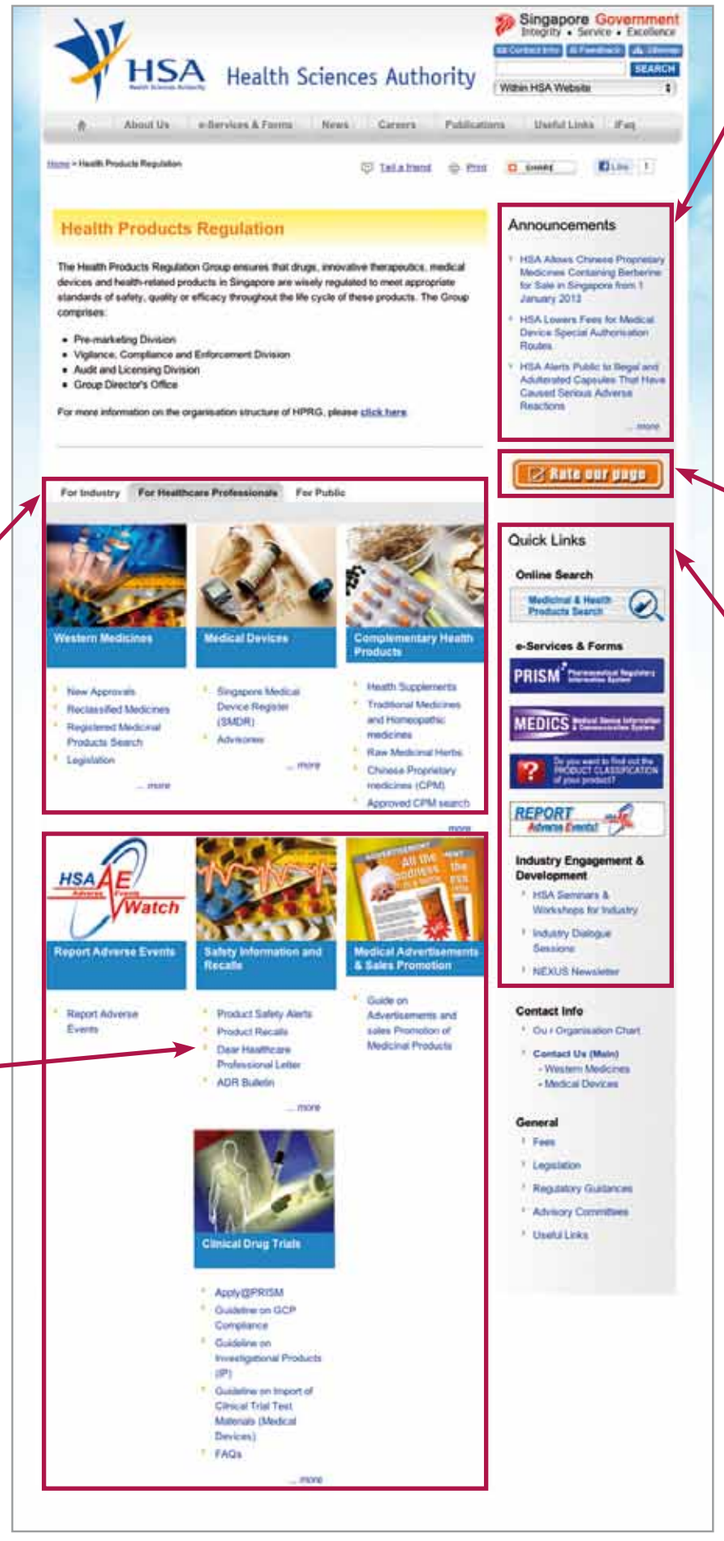
Please refer to the screenshots provided for a quick summary of the new features you can find on the new home page.

Your feedback is important

We hope that the pilot revamp will improve your surfing experience at our website and also allow you to find essential information quickly. Please visit our website at *http://www.hsa.gov.sg* and click on the "Health Products Regulation" icon to view our new homepage. Should you have any feedback and comments, please click the "Rate our page" button to share your views.

Clicks on tabs to toggle between interest groups

Quicklinks for easy access to information



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List of Dear Healthcare Professional Letters (DHCPL) issued by HSA, pharmaceutical and medical device companies

Summary of Dear Healthcare Professional Letters issued by HSA and/or pharmaceutical and medical device companies from December 2011 to November 2012. For details, please log on to MOHAlert via your professional board's website.

12 Dec 2011	–	Importance of assessing renal function in patients treated with Pradaxa® (dabigatran etexilate) [Boehringer Ingelheim]
15 Dec 2011	–	Direct healthcare professional communication on supply and safety concerns for CAELYX® (pegylated liposomal doxorubicin) 20 mg vials for injection [Janssen]
15 Dec 2011	–	VELCADE® (bortezomib) 3.5mg powder for solution for injection [J&J]
15 Dec 2011	–	The switching of manufacturing source for Busulfex injection® 6mg/ml [Kyowa Kirin]
19 Dec 2011	–	Good Manufacturing Practices (GMP) Deficiencies at Ben Venue Laboratories Inc, USA [Pfizer]
30 Dec 2011	–	Important information on the regulation of medical devices in Singapore [HSA]
5 Jan 2012	–	Direct healthcare professional communication on potential risks of cardiovascular and renal adverse events in patients with type 2 diabetes and renal impairment and/or cardiovascular disease treated with aliskiren [Novartis]
6 Feb 2012	–	Recent series of serious adverse event (SAE) reports suspected to be related to illegal sexual enhancement health products [HSA]
22 Feb 2012	–	Restriction of use of dronedarone (Multaq®) [HSA]
5 Mar 2012	–	Serious hypersensitivity reactions and acute pancreatitis reported with Onglyza® (saxagliptin); Label update for Onglyza® (saxagliptin) [BMS & AstraZeneca]
8 Mar 2012	–	Intravenous route as the only appropriate route for administration of VELCADE® (bortezomib) [J&J]
9 Mar 2012	–	HSA recalls Albumex 20® (20% albumin) from CSL Biotherapies as a precautionary measure [HSA]
9 May 2012	–	Feedback sought on Low-Volume-Low-Cost medical devices [HSA]
1 Jun 2012	–	Victrelis® capsule 200mg: Important drug interaction [SOL Limited]
19 Jun 2012	–	Important information on Pharmaceutical Innovations Inc's 'Other-Sonic Generic Ultrasound Transmission Gel' [HSA]
12 Jul 2012	–	Continuation of the restricted access programme for aprotinin (Trasylol®) [HSA]
13 Jul 2012	–	Increase in local reports of serious skin reactions related to strontium ranelate (Protos®) [HSA]
13 Jul 2012	–	Recall of 2 batches of Anzatax Injection Concentrate 300mg/50ml [Hospira]
7 Aug 2012	–	Recall conducted overseas of 2 batches of Artesunate (Dihydroartemisinin-12-A-Succinate) Powder For Injection 60mg [HSA]
10 Aug 2012	–	Alert on counterfeit Ligaclip® Extra Ligating Clip Cartridges [HSA]
10 Aug 2012	–	Recall of Thymoglobuline 5 mg/ml Powder for Concentrate for Solution for Infusion [Sanofi-aventis]
25 Sep 2012	–	Voluntary recall of selected batches of Sanofi Pasteur Vi polysaccharide typhoid vaccine, Typhim Vi® with potentially low antigen content [Sanofi Pasteur]
5 Oct 2012	–	Risk of atypical fracture with Prolia® (denosumab) [GSK]
19 Nov 2012	–	Recommended storage conditions at 2 to 8°C for Neupro® (rotigotine) [UCB]

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Safety update on proton pump inhibitors

Clostridium difficile-associated diarrhoea, fracture risk and drug interaction with methotrexate

A review of important safety information related to the class of proton pump inhibitors (PPIs) has been completed by HSA recently, and the local package inserts will be strengthened to include these new safety updates. The PPIs registered in Singapore include omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole, all of which are classified as Prescription Only Medicines (POM). Their indications include gastro-oesophageal reflux disease, acid-related dyspepsia, gastric and duodenal ulcers, and reflux oesophagitis. In addition, omeprazole oral solid preparations containing not more than 20mg may be sold as Pharmacy Only (P) medicines to patients aged 18 years and above, with a maximum dose of 20mg daily and maximum supply for up to 14 days.

a) Clostridium difficile-associated diarrhoea (CDAD)

Earlier this year, the US Food and Drug Administration (FDA) reviewed reports from the Adverse Event Reporting System (AERS) and medical literature for cases of CDAD in patients undergoing treatment with PPIs.[1] It was reported that the risk of *C. difficile* infection or disease ranged from 1.4 to 2.75 times higher among PPI users compared to non-PPI users. Although data on the relationship between the risk of *C. difficile* infection or CDAD and PPI dose and duration of use remains limited, the weight of the evidence suggests a positive association between the use of PPIs and *C. difficile* infection and disease, including CDAD.

In view of this information, the FDA issued a class warning that use of PPIs may be associated with an increased risk of CDAD.[1] Symptoms include watery stool, abdominal pain and fever, which may develop into more serious intestinal conditions. Physicians were reminded to consider a diagnosis of CDAD in patients taking PPIs who develop diarrhoea that does not improve.

b) Risk of fractures

A review by the European Medicines Agency's Pharmacovigilance Working Party (PhVWP) of data from clinical trials and observational studies concluded that PPIs, especially if used in high doses and over long duration (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in the presence of other recognised risk factors such as osteoporosis or use of corticosteroids.[2] This was supported by results from two meta-analyses of published pharmacoepidemiological studies (Table 1).[3,4] However, the published studies were inconsistent in terms of the magnitude of the risk and the duration of time-to-event, and varied with respect to the potential confounders that were adjusted for.

Table 1. Adjusted odds ratio for any fracture, hip fracture and spine fracture with PPI use

Type of fracture	Adjusted Odds Ratio Meta-analysis by Kwok *et al*[3]	Meta-analysis by Eom *et al*[4]
Any fracture	1.20 (95% CI 1.11–1.30)	1.29 (95% CI 1.18–1.41)
Hip fracture	1.23 (95%CI 1.11–1.36)	1.31 (95% CI 1.11–1.54)
Spine fracture	1.50 (95% CI 1.32–1.72)	1.56 (95% CI 1.31–1.85)

The US FDA had also issued a similar alert on an increased risk for osteoporosis-related fractures of the hip, wrist, or spine with PPI therapy.[5] This was based on its review of published epidemiological studies that used administrative claims data, although it acknowledged that randomised clinical trials of PPIs have not found an increased fracture risk. Patients were advised to use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

c) Drug interaction with methotrexate

In October 2012, Health Canada issued an alert on a potential interaction between PPIs and methotrexate.[6] The use of these two products at the same time by patients may increase the amount of methotrexate in the blood, leading to health risks such as renal failure, low haematologic cell count, stomatitis, infections, and diarrhoea. While a definite association between PPI use and an increase in blood levels of methotrexate has not been confirmed, there have been a number of studies suggesting a possible interaction between PPIs and methotrexate. As such, Health Canada considers the potential for an increased risk of methotrexate side effects as very likely and will update the Canadian monographs of PPI products to include information on this potential interaction.

The warning on concomitant use of PPIs with methotrexate has also been updated in the US prescribing information for PPI products to highlight that literature suggests that this drug-drug interaction may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities.

HSA's actions and advisory

To date, HSA has not received any local adverse reaction reports on CDAD or fractures associated with the use of PPIs, nor any reports involving a drug interaction between methotrexate and PPIs. Thirteen reports of diarrhoea with use of omeprazole or pantoprazole have been received, but none of them have specifically been attributed to CDAD.

HSA has reviewed the available information on the three safety issues highlighted above and will be working with the product licence holders of the various PPI products to strengthen the local package inserts to include warnings and precautions to address these concerns.

Healthcare professionals are advised to take into consideration the above safety information when prescribing PPIs, and to inform their patients to seek medical attention for diarrhoea lasting longer than three days or accompanied by blood or high fever. PPIs, in general, should be prescribed at the lowest dose and for the shortest duration of therapy appropriate to the condition being treated. A temporary withdrawal of the PPI may be considered in some patients receiving treatments with high-dose methotrexate.

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

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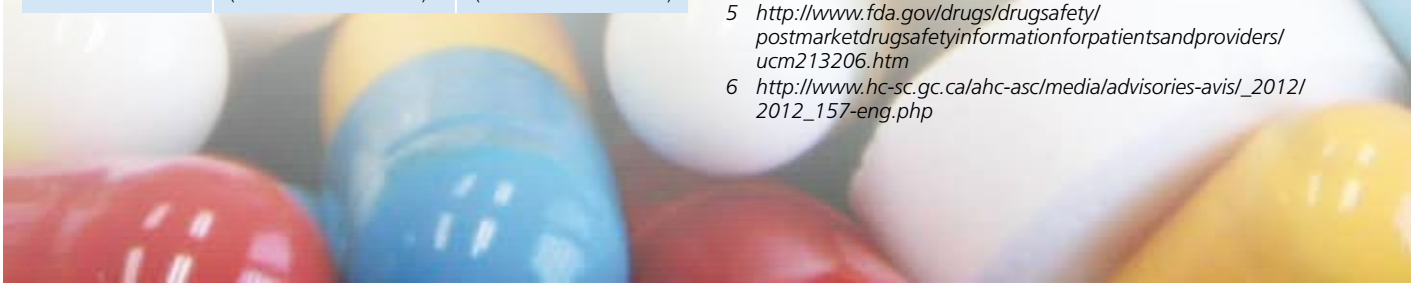

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HSA hosts pharmacovigilance training course for Asia-Pacific countries

The month of October marked a milestone event when over 40 participants, including more than 20 overseas delegates from ASEAN and the Asia-Pacific region (Brunei, Cambodia, Hong Kong, Korea, Indonesia, Malaysia, New Zealand, Sri Lanka, Thailand and Vietnam) gathered in Singapore to attend the WHO-HSA Inter-regional Pharmacovigilance (PV) Training Course held from 10 to 12 October 2012. This training was jointly organised by the World Health Organisation (WHO) and HSA, with participation from the Uppsala Monitoring Centre (UMC). Covering a series of advanced topics, it is a follow-up of the WHO-UMC-HSA Basic Pharmacovigilance Training conducted in 2010. The course aimed to equip participants with the necessary skills to further strengthen PV capabilities in the region, with particular focus on pharmacoepidemiology and data mining. These objectives were well aligned with WHO's and UMC's continual drive to communicate the importance of drug safety and PV among countries.

International and local panel of speakers

Renowned experts in the areas of pharmacoepidemiology and data mining chaired the training sessions. These comprised Professor Hubert Leufkens, Professor of Pharmacoepidemiology, Utrecht Institute of Pharmaceutical Sciences and Chairman of the Dutch Medicines Evaluation Board, Dr Ruth Savage, Senior Medical Assessor at the Centre for Adverse Reactions Monitoring (CARM), New Zealand PV Centre and Senior Lecturer at Christchurch School of Medicine, University of Otago, New Zealand, and Ms Jeanette Johansson, Team Manager of UMC's Analysis Team. Ms Dorothy Toh, Director of Vigilance Branch, HSA, also presented on HSA's PV and pharmacogenetics initiatives. The occasion was also graced by the attendance of Mr Daisuke Koga from the WHO.

Key topics covered

As technological advancements continue to facilitate the collection of large amounts of health data, regulators are turning to data mining tools and pharmacoepidemiology capabilities to analyse adverse drug reaction databases. Participants gained valuable insights on various aspects of data mining, including its application in signal detection, the different methods available, as well as the interpretation of results. These were further illustrated with examples of actual signals picked up through data mining encountered by the speakers in the course of their work. Participants also had a hands-on session using VigiMine™, a powerful data mining tool which analyses Individual Case Safety Reports (ICSR) from WHO.

Apart from these, the training also covered pharmacoepidemiological principles, methods and applications. An opportunity to apply this knowledge was provided as participants worked on case studies and engaged in group discussions to formulate their own study designs. This was followed by a lively presentation session as participants critically reviewed one another's work.

Participants of the course were also introduced to pharmacogenomics, an area which is receiving increasing attention. Participants learnt about how pharmacogenomics research is currently applied in PV work, the great potential that pharmacogenomics holds, and how this could be harnessed in the ongoing pursuit for patient safety.

Moving forward

The training was well received by participants, and provided a unique opportunity for delegates across the region to interact and share their experience in PV work. As Associate Professor John Lim, CEO of HSA, shared in his opening speech, PV is a rapidly evolving and dynamic discipline, and it is crucial that we continue to develop and expand our capabilities. It is hoped that, armed with new knowledge and perspectives, participants would be empowered to enhance PV capabilities in their countries, and improve drug safety in the region. This sentiment was shared by the participants, who found the course well-organised and informative, and looked forward to applying the concepts gleaned from the lectures and breakout sessions to their respective areas of work.

Changes to the safety-related product label amendments webpage

With effect from November 2012, the details of the safety-related amendments made to the local package inserts will no longer be published on the HSA website. A list of the products with recently approved safety-related label changes will still be provided at the following weblink: *www.hsa.gov.sg/label_amend*

Healthcare professionals are advised to access the Infosearch function at *www.hsa.gov.sg/infosearch* to look for the package inserts with the latest safety-related changes. Please note that there may be a lag time in the availability of the package insert which reflects the latest change(s).

Recent product safety-related articles published on HSA website

HSA's electronic publications of product safety-related articles are available at *http://www.hsa.gov.sg*. All healthcare professionals are encouraged to visit HSA's website to access the latest product safety information.

1 HSA alerts public on Field Safety Corrective Action related to affected batches of Nuvo/Nuvo Lite Oxygen Concentrators (27 July 2012)

2 HSA alerts public to adverse reactions related to the consumption of adulterated health products, including a fatal case (3 October 2012)

3 HSA updates on the recent outbreak of meningitis in the US (17 October 2012)

Look out for the inaugural publication of the Medical Device Alert circular bringing you updates on recent Field Safety Corrective Actions (FSCA).

Chinese Proprietary Medicines containing berberine will be allowed for sale in Singapore from 1 January 2013

Healthcare professionals have a part to play in the vigilance of potential adverse reactions

HSA would like to inform healthcare professionals that it will allow the sale of Chinese Proprietary Medicines (CPM) containing berberine (小檗碱) in Singapore from 1 January 2013 following a prohibition of such sales since 1978.

Berberine is an alkaloid present naturally in herbs such as *Rhizoma coptidis* (黄连) and *Cortex phellodendri* (黄柏) that are commonly used in Traditional Chinese Medicine (TCM) for their "heat-clearing" and "dampness-drying" (清热燥湿) properties in the body.

Adverse effects such as nausea, vomiting and rashes have occasionally been reported with the use of berberine. The prohibition of the use of berberine, as controlled under the Poisons Act, was implemented by MOH in 1978, arising from local safety concerns that berberine could cause kernicterus, severe jaundice and brain damage in glucose-6-phosphate dehydrogenase (G6PD) deficient babies.

Review of prohibition on berberine

Over the past years, HSA, together with its expert committees, has been monitoring the situation and conducting ongoing scientific reviews on the safety profile of berberine. This includes literature review of scientific publications on the safety of berberine, and adverse reactions reported in other countries. The feedback from the TCM community and developments in the local regulatory landscape were also considered in the review of berberine.

The latest review conducted by the Berberine Expert Panel indicates that there are no major safety concerns when berberine is used appropriately under a controlled regulatory regime, **but it should still be avoided in infants, G6PD-deficient individuals of all ages, pregnant and breastfeeding women.**

Based on the recommendations of the Berberine Expert Panel and taking into consideration that there are sufficient safeguards in-place over the years (which include the pre-market approval of CPM products and the compulsory registration of TCM practitioners), HSA, in consultation with MOH, will adopt a phased approach in the lifting of the prohibition on berberine use in Singapore. For a start, the use of CPM containing berberine, (eg, finished dosage forms such as capsules, oral liquid preparations, powders and granules used by TCM practitioners) would be allowed with effect from 1 January 2013. In the absence of major safety issues, HSA will review the possible further lifting of prohibition on Chinese herbs containing berberine by 2015.

Follow-up actions and call to reporting of adverse reactions

To safeguard public health, CPM containing berberine will be subjected to the current regulatory regime whereby HSA will review the safety and quality of these preparations before they are placed in the local market. Additional labelling requirements, in the form of cautionary statements to warn against use in infants, G6PD-deficient individuals of all ages, pregnant and breastfeeding women, will be imposed on these products.

With the lifting of the ban, HSA will continue to monitor the situation closely for any occurrence of adverse reactions. HSA views healthcare professionals as important partners in vigilance and we seek your assistance in closely monitoring patients whom you are aware of consuming berberine-containing CPM especially young children. It is recommended that healthcare professionals obtain a thorough medication history of the patient including the consumption of complementary medicines to ascertain if any adverse reaction reported could be related to such products.

HSA also strongly encourages healthcare professionals to report adverse reactions suspected to be related to the consumption of berberine-containing CPM to the Vigilance Branch of HSA.

Please send your enquiries, comments and suggestions to:

Vigilance Branch
Health Products Regulation Group
Health Sciences Authority
11 Biopolis Way, #11-01,
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 30 Nov 2012.