

Monitoring the safety profile of Influenza A/H1N1(2009) vaccines

The Health Sciences Authority (HSA) has approved the use of two brands of Influenza A/H1N1 (2009) vaccine, namely Panvax® (CSL) for adults and children 6 months old and above and Pandemrix® (GSK) for adults 18 years and above. With the roll-out of the H1N1 influenza vaccination in Singapore, HSA would like to emphasize the importance of being vigilant to potential and new safety signals arising from the use of Influenza A/H1N1(2009) vaccines.

Background on H1N1 influenza vaccine safety

The interim findings of data from ongoing clinical trials and the post-marketing experience in countries where H1N1 vaccination is being implemented suggest that these vaccines are well tolerated and the adverse effect profile is similar to that of seasonal flu vaccines.

As with any medicine/vaccine, there are unexpected or rare serious adverse events that may be associated with the use of the H1N1 vaccines, especially when they are used on a massive scale and for different groups of patients. The Ministry of Health (MOH) and HSA will be intensifying the surveillance activities, to closely monitor the safety and usage of H1N1 vaccines in our local population.

Healthcare professionals are required to notify the National Immunisation Registry (NIR) of all patients who have been vaccinated with the H1N1 vaccines and to report all suspected serious vaccine adverse events (VAE) to HSA. VAE may occur within the same day of administration of the vaccine or after a longer period of time e.g. 3 – 6 months later. Healthcare professionals are encouraged to report any suspected serious adverse events even if you are unsure whether the vaccine could have caused the event as follow-up investigations

will be conducted by HSA to assess the causality. The information provided by you will allow a more accurate computation of the incidence rate of VAE in Singapore, and also potentially help determine whether any specific patient groups may be at a higher risk of serious adverse events.

A) Vaccine adverse event (VAE) reporting

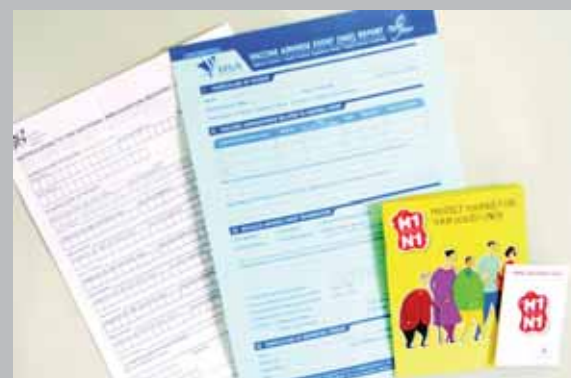
Healthcare professionals are strongly encouraged to adhere to the following vigilance guidelines for the safety monitoring of H1N1 vaccines:

- all ***fatal and life-threatening events***, suspected to be associated with H1N1 vaccination are to be reported as soon as possible, preferably within 24 hours
- all other ***serious*** adverse event reports and ***adverse events of special interest (AESI)*** such as Guillain-Barré syndrome are to be reported as soon as possible or within 7 days. (See table 1 for definition of serious adverse events and table 2 for examples of AESI).
- the brand name should be reported and batch number included, if available.

Table 1: Definition of serious adverse events

Serious adverse events include those which:

- are life-threatening or fatal
- require in-patient hospitalisation or prolong existing hospitalisation
- cause persistent incapacity or disability
- cause birth defect
- are medically significant



NIR form, VAE form, Patient education pamphlet & Patient vaccination card

Table 2: Examples of adverse events of special interest (AESI)

Serious adverse events of interest (AESI) that have been associated historically with the use of vaccines include:

- anaphylaxis
- Guillain-Barré syndrome
- Bell's palsy
- demyelinating disorders
- neuritis
- convulsion
- encephalitis
- thrombocytopenia
- vasculitis
- vaccination failure

There are three platforms that may be used for the submission of VAE reports:

- manual reporting through completion of the HSA VAE reporting form and faxed to 6478 9069/6478 9038 or by phone at Tel: 6866 3538/ 6866 3548
- online reporting through the VAE form posted on the HSA website at http://www.hsa.gov.sg/ae_online
- reporting through the Adverse Drug Reactions/Drug Allergy module of the Critical Medical Information Store (CMIS) available in the Electronic Medical Record (EMR) of public health

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Suspension of sales of dextropropoxyphene-containing products

The Health Sciences Authority (HSA) would like to inform healthcare professionals that the sales of dextropropoxyphene-containing products have been suspended effective from 9 November 2009.

Dextropropoxyphene, a weak synthetic opioid analgesic, was registered by HSA since 1991 for the treatment of mild to moderate pain. It was marketed under two brands namely Dolpoxene® (Singapore Pharmaceutical Pte Ltd) which contains only dextropropoxyphene and Dolpocetmol® (Singapore Pharmaceutical Pte Ltd) which contains a combination of dextropropoxyphene and paracetamol.

HSA's risk-benefit assessment of dextropropoxyphene

HSA has been closely monitoring the safety profile of dextropropoxyphene following withdrawal of dextropropoxyphene-containing products by UK in 2005¹ and the European Union² in June 2009. Based on the assessment of the data available to-date, HSA and its Pharmacovigilance Advisory Committee (PVAC) have concluded that the risk of dextropropoxyphene outweighs its benefits in the treatment of mild to moderate pain.

The review took into consideration its limited therapeutic efficacy as compared to commonly used analgesics, the availability of other therapeutic alternatives such as paracetamol, NSAIDs and opioids, the potential risk of fatal overdose associated with dextropropoxyphene as well as the risk-benefit assessments of other

regulatory agencies. In addition, it has also been highlighted in several literature articles that norpropoxyphene, the metabolite of dextropropoxyphene, has been associated with cardiac toxicities.^{3,4}

The potential risk of fatal overdose with dextropropoxyphene and cardiac toxicities associated with its metabolite, norpropoxyphene are considered unacceptable in view of dextropropoxyphene's modest efficacy. As such, the importation, sales and marketing of Dolpoxene® and Dolpocetmol® at the wholesale level was suspended with effect from 9 November 2009.

Healthcare professionals are advised not to start new patients on dextropropoxyphene and to consider alternative treatment options for patients currently taking dextropropoxyphene products for pain relief.

References

1. Press release. Mhra withdraws the pain killer Co-proxamol. <http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON002065>
2. PRESS RELEASE. EMEA recommends withdrawal of dextropropoxyphene-containing medicines <http://www.emea.europa.eu/pdfs/human/press/pr/40106209en.pdf>
3. Chan GJ, Matzke GR. Effects of renal insufficiency on the pharmacokinetics and pharmacodynamics of opioid analgesics. *Drug Intell Clin Pharm.* 1987; 21:773 - 783
4. Nagar S, Raffa RB. Looking beyond the administered drug: Metabolites of opioid analgesics. *The Journal of Family Practice* 2008; Vol 57, No. 6: S25 -S32

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institutions. For this platform, for the field on 'generic name' of the suspected drug causing the adverse event, please enter 'H1N1 2009 vaccine' and key in the brand name accordingly, i.e. Panvax H1N1 or Pandemrix H1N1.

B) Notification of vaccine particulars to NIR

Submission of vaccinee particulars, including the batch number of the vaccine to the NIR is required to determine the population exposure. The submission should preferably be done as soon as possible, not later than one week. Notification of the H1N1 vaccine administration may be done through the following options:

- a) mail the completed hard copy of the NIR form (provided in the information kit of your vaccine order) with the self-addressed envelope provided
- b) notification via the Health Professional Portal (HPP) at <https://www.hpp.moh.gov.sg>.

For notification via HPP, click on "Notify NIR on H1N1 Vaccination" icon to log in to the secured webpage with MCR number and password. On the right hand side of the webpage, choose under "Applications" the icon, "Access NIR to notify H1N1 vaccination". Follow the instructions provided on the NIR website to download the Microsoft Excel template. Compile patient details and upload onto NIR registry. Records of up to 100 patients may be submitted each time.

C) Other relevant patient information materials

All vaccinees receiving the H1N1 vaccine should be supplied with a vaccination card which details the vaccination date, brand name and batch number of the H1N1 vaccine that was administered. The information on the vaccine card should be completed by a healthcare professional. Hard copies of the VAE forms, NIR reporting forms, vaccination cards and patient medication guides will be provided to you in the Vaccine Information Kit that accompanies each vial/syringe of the vaccine.

Local experience with the H1N1 influenza vaccine, Panvax®

As of 8 December 2009, an estimated 370,000 doses of Panvax® and about 100 doses of Pandemrix® have been distributed locally. Singapore first began the immunisation programme with Panvax®

on 3 November 2009 followed by Pandemrix® on 26 November 2009. Up to 8 December 2009, 80 reports of suspected adverse events associated with the vaccine have been received by the Vigilance branch.

The adverse events (AEs) received for Panvax® vaccine appear similar to the safety profile for seasonal flu vaccines. They comprise mainly of non-serious hypersensitivity reactions such as rash, itch, swollen eyelids, injection-site reactions and influenza-like symptoms. Other non-serious reports include dizziness, fainting, headache and paraesthesia.

To date, 10 reports were assessed as serious by the reporting physicians. Of these, eight reports have been reviewed and followed up by HSA and they include three reports of allergic reactions of varying severity including one case of anaphylaxis, a case of exacerbation of pre-existing scleritis, a case of persistent vomiting, a case of Sweet's syndrome, a case of dystonia and a case of bronchospasm occurring five hours after vaccination. Five of these patients have pre-existing allergic medical conditions such as asthma or are known to be allergic to certain medications. All the eight patients have since recovered or are recovering. The other two of the other serious reports are currently still under review. The Vigilance Branch will provide further updates as more information becomes available.

It is important to note that while serious adverse events may be reported in association with the vaccines, the causality based on isolated cases of individual events cannot be definitely established as there are no confirmatory tests for diagnosing an adverse event. In certain instances, these serious adverse events may be coincidental occurrence of a disease that is not caused directly by the vaccine and further observations would be needed to confirm otherwise.

Conclusion

The Vigilance Branch of HSA seeks the co-operation of all healthcare professionals in adhering to the above guidelines on the reporting of VAE and notification of vaccinees to NIR. Healthcare professionals can access http://www.hsa.gov.sg/h1n1_vaccines for updates on the safety profile of the H1N1 vaccines.

New online search on illegal health products

Illegal health products are a growing health problem that pose a real and direct danger to consumers both locally and globally. As evidenced by local reports of members of the public unwittingly consuming adulterated products, consumers are frequently innocent victims of illegal peddlers and websites as they are not equipped with sufficient information to make an informed decision on their purchases.

HSA has developed a database to facilitate the identification of illegal health products by healthcare professionals and members of the public. The illegal health products database provides online access to information on illegal health products. It stores product information and pictures of illegal health products that have been seized by or reported to HSA, and include products which have been tested to contain adulterants. Although not an exhaustive list, the database currently contains information on about 200 illegal health products. The database will be updated periodically as HSA uncovers more illegal health products.

Accessing the database

The illegal health products database can be accessed from HSA's homepage at <http://www.hsa.gov.sg> following the steps below (refer to screenshots):

- Click on the **"Illegal Health Products can KILL"** button on HSA's homepage



- A new webpage will appear, click on **"Illegal Health Products Found in Singapore"**

- Search by product name in English and/or Chinese, or by going through the alphabetical listing of the product names in the database

- Search by product characteristics such as dosage form (eg, capsule, tablet), shape, marking and/or colour (especially useful if product identity, such as the name of the product is unknown)

Product Name	Dosage Shape	Dosage Form Marking	Dosage Colour	Adulterant Type	Thumbnail
De Guo Jin Gang Pen (德國金剛牌)	-	-	Brown	Lignocaine	
Di Er Dai Ye Lang Shen 2000mg Capsule (第二代夜狼神)	Oblong	-	Maroon	Sildenafil	
Di Liu Dai Yi Fan Dan Tian Liang 2000mg Yao Shi Jiao Nang (第六代易反丹天良 2000mg 藥石交丸)	Oblong	空源刺造	Black Red	Sildenafil Tadalafil	
Ding Xin Brand Yilichen 0.4g Capsule (定心牌益力臣)	Oblong	紅力牌	Orange Grey	Sildenafil	
Dong Fang Fu Bai 800mg Tablet (東方富白 800mg 藥片)	Diamond	800mg	Brown	Sildenafil	
Dripfarm Brand Emperor Capsule 0.5g (滴發牌皇帝藥丸)	Oblong	皇帝牌 (SUPER)	Blue Transparent	Sildenafil	

- Please contact the Enforcement Branch at **6866 3485** or **email hsa_is@hsa.gov.sg** should you require assistance to navigate the online database. You may also use this channel to report an illegal health product.

Conclusion and HSA's advisory

In addition to using the Illegal Health Product Online Search as a source of reference, HSA strongly encourages healthcare professionals to report adverse events suspected to be related to illegal health products to the Vigilance Branch of HSA. HSA hopes that this initiative will strengthen the partnership between HSA, healthcare professionals and members of the public to minimise the purchase of illegal health products on the local market and to safeguard public health.

Important Drug Interactions

HSA would like to highlight the recent findings of significant drug interactions which healthcare professionals need to be aware of. Specifically this relates to the interaction between clopidogrel and proton pump inhibitors (PPI), as well as the interaction between colchicine, P-glycoprotein (P-gp) and strong CYP3A4 inhibitors. Healthcare professionals are reminded to report adverse events suspected to be related to the above interactions to the Vigilance Branch of HSA.



A) Interaction between clopidogrel and proton pump inhibitors (PPI)

Clopidogrel is an antiplatelet prodrug used for the prevention of atherothrombotic events. One of the pathways for forming the active metabolite involves the CYP2C19 isoenzyme. Several studies, including large clinical outcome studies, have shown that the effectiveness of clopidogrel is diminished in patients with a polymorphism of the CYP2C19 allele that results in reduced activity of this enzyme.

Some reports suggest that use of certain PPI may make clopidogrel less effective by inhibiting the enzyme that converts clopidogrel to the active form of the drug while others do not suggest this effect. PPI decrease stomach acid and are used to treat frequent heartburn and stomach ulcers. Clopidogrel can irritate the stomach so PPI are commonly used with clopidogrel to help reduce this irritation.^{1,2}

Clopidogrel is available in Singapore as Plavix®, Plagril®, Clopidogrel Winthrop®, Apo-clopidogrel® and in combination with aspirin as Co-Plavix®. There are several PPI available in Singapore, namely, omeprazole, pantoprazole, esomeprazole, rabeprazole and lansoprazole.

Recent published report in JAMA

In March 2009, the results of a retrospective cohort study that investigated the risk of all-cause mortality or re-hospitalisation associated with use of clopidogrel with or without PPI following acute coronary syndrome (ACS) were published in JAMA.

Of 8,205 patients taking clopidogrel after discharge, 63.9% (n=5,244) were prescribed PPI at discharge, during follow-up, or both while 36.1% (n=2,961) were not prescribed PPI. Death or re-hospitalisation for ACS occurred more frequently in patients taking clopidogrel plus PPI (29.8%; n=1,561) than in patients taking clopidogrel without PPI (20.8%; n=615). In multivariable analyses, use of clopidogrel plus PPI was

associated with an increased risk of death or re-hospitalisation for ACS compared with use of clopidogrel without PPI

(adjusted odds ratio [AOR], 1.25; 95% confidence interval [CI], 1.11-1.41). Among patients taking clopidogrel after hospital discharge and prescribed PPI at any point during follow-up (n=5,244), periods of use of clopidogrel plus PPI (compared with periods of use of clopidogrel without PPI) were associated with a higher risk of death or re-hospitalisation for ACS (adjusted hazard ratio, 1.27; 95% CI, 1.10-1.46).³

The results of this study support the findings from prior platelet studies demonstrating that PPI reduce the anti-platelet effects of clopidogrel, possibly by sharing common metabolic pathways mediated by cytochrome P450 isoenzymes (i.e. CYP2C19).

Local Actions

To date, HSA has not received local adverse reaction reports of drug interactions with PPI or a reduction in efficacy associated with Plavix®.

The local package insert of Plavix® has recently been updated to inform of the lower systemic exposure to the active metabolite of clopidogrel and diminished antiplatelet responses, as well as the exhibition of higher cardiovascular event rates following myocardial infarction, in patients with genetically reduced CYP2C19 function than do patients with normal CYP2C19 function. Hence, concomitant use of clopidogrel with drugs that inhibit CYP2C19 is discouraged. In addition, although the evidence of CYP2C19 inhibition varies within the class of PPI, clinical studies suggest an interaction between clopidogrel and possibly all members of this class of drugs. Therefore, it is recommended that the concomitant use of PPI with clopidogrel be avoided unless absolutely necessary.

B) Interaction between colchicine and P-glycoprotein (P-gp) or strong CYP3A4 inhibitors

Colchicine had been registered in Singapore for the treatment and prophylaxis of acute gout attacks. There are currently three generic colchicine products available locally namely, Colchicine Tablet® 500 mcg, Colchicine Tablets BP® 500 mcg and Colcitem Tablet® 0.6 mg.

Safety data from US Food and Drug Administration (FDA)

An analysis of safety data for colchicine from spontaneous reports to FDA, the literature and company sponsored clinical studies revealed 169 deaths associated with the use of oral colchicine. Of these, 117 cases occurred within the standard therapeutic doses of colchicine (≤ 2 mg/ day). Sixty out of these 117 cases had

clarithromycin, a CYP3A4 inhibitor, as a concomitant medication. The findings from this analysis suggested that drug interactions affecting gastrointestinal absorption and/or hepatic metabolism of colchicine play a central role in the development of colchicine toxicity.

The absorption of colchicine from the gastrointestinal tract is limited by the multidrug resistance efflux transporter P-glycoprotein (P-gp), while the metabolism of colchicine to inactive metabolites is catalysed by intestinal and hepatic cytochrome P450 CYP3A4. Colchicine is primarily eliminated by hepatobiliary excretion through the stool. Renal excretion accounts for 10% to 20% of colchicine elimination in patients with normal renal function. The theoretical risk of colchicine toxicity through the modulation of P-gp and CYP3A4 activity is further supported by the presence of fatal and non-fatal cases of colchicine toxicity reported in literature with

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Compliance to the safety monitoring protocols of the 'RevAssure Programme' of Lenalidomide (Revlimid®)

On 7 September 2009, a 'Compliance Communication' letter was issued to healthcare professionals who purchase Revlimid® by the *Compliance Branch of HSA to inform them of the safety monitoring protocols that have been imposed on the prescribing and dispensing of lenalidomide (Revlimid®), a potentially teratogenic drug marketed by Celgene Pte Ltd. The letter also sought the co-operation of healthcare professionals to comply to the safety monitoring protocols when prescribing lenalidomide to their patients.

Background on lenalidomide and thalidomide

Lenalidomide (Revlimid®), a prescription only medicine, is an immunomodulatory drug that is structurally related to thalidomide and is licensed for use in combination with dexamethasone for the treatment of patients with multiple myeloma who have received at least one other prior therapy. Revlimid® has been approved in Singapore on 23 June 2009 but due to its potential teratogenicity, is subject to safety monitoring protocols to be complied with prior to prescription and dispensing of the drug.

Thalidomide is a known human teratogen that causes severe life-threatening birth defects. As Revlimid® is structurally related to thalidomide, a teratogenic effect cannot be ruled out when it is taken during pregnancy. An embryo-foetal development study in non-human primates indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy, similar to the birth defects observed in humans following exposure to thalidomide during pregnancy. Revlimid® is therefore contraindicated in pregnant women.

Conditions of HSA Approval and Registration of Revlimid® – the RevAssure Programme

The RevAssure is a programme implemented by Celgene, as mandated by HSA to minimize the risk of foetal exposure associated with the use of Revlimid®, in view of its potential teratogenic effect. As part of the safety protocol, healthcare professionals can only prescribe and dispense Revlimid® upon fulfilling the conditions of the RevAssure programme. Extracts of important requirements under the RevAssure**



programme are as follows:

- Registering with the RevAssure programme to undertake the roles and responsibilities as described for healthcare professionals
- Obtaining patients' consent for therapy to confirm their understanding of the risks and to obtain their agreement to comply with requirements of the programme
- Conducting pregnancy tests for women of childbearing potential
- Counselling certain patient groups to use effective contraceptive methods

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

Advisory to healthcare professionals

As adherence to the requirements of the RevAssure programme is essential to prevent foetal exposure to Revlimid®, the Compliance Branch of HSA seeks the co-operation of healthcare professionals to ensure the successful implementation of the RevAssure programme.



[*Note: In January 2009, HSA established the Compliance Branch to streamline the interface between HSA and health product companies which allows a seamless transition from pre-marketing approval stage of a health product to the post-marketing regulated stage.]

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concomitant use of other CYP3A4 and P-gp inhibitors such as cyclosporine, erythromycin and calcium channel blockers eg, verapamil and diltiazem. Other examples of P-gp and strong CYP3A4 inhibitors include telithromycin, ketoconazole, itraconazole, HIV protease inhibitors, and nefazodone.⁴

Regulatory actions Taken in the US

Based on this information, FDA concluded that there is a risk for severe drug interactions in certain patients treated with colchicine and concomitant P-gp or strong CYP3A4 inhibitors. In view of this, FDA recommended that P-gp or strong CYP3A4 inhibitors not be used in patients with renal or hepatic impairment who are currently taking colchicine. Furthermore, FDA also recommended that healthcare professionals consider a dose reduction or interruption of colchicine in patients with normal renal and hepatic function if treatment with a P-gp or strong CYP3A4 inhibitor is required.⁴

Local Actions

To date, HSA has not received any local adverse drug reaction reports of colchicine toxicity associated with concomitant use of P-gp and strong CYP3A4 inhibitors. Healthcare professionals are advised to take into consideration the above safety information when prescribing colchicine with a P-gp or strong CYP3A4 inhibitor.

References

- <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProvidersDrugSafetyInformationforHealthcareProfessionals/ucm079520.htm>
- <http://www.emea.europa.eu/humandocs/PDFs/EPAR/Plavix/32895609en.pdf>
- JAMA. 2009;301(9):937-944. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome
- <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProvidersDrugSafetyInformationforHealthcareProfessionals/ucm174315.htm>

Tinzaparin (Innohep®) and risk of death in the elderly with renal impairment



The Vigilance Branch of HSA would like to bring to the attention of healthcare professionals, the results of the clinical study, Innohep® in Renal Insufficiency Study (IRIS), suggesting that tinzaparin (Innohep®, LEO Pharma) may increase the risk for death, compared to unfractionated heparin (UFH) when used to treat elderly patients with renal insufficiency.

Innohep® is a low molecular weight heparin indicated for treatment of deep-vein thrombosis (DVT) and pulmonary embolism (PE) as well as for the thromboprophylaxis in patients with high risk of venous thromboembolism (VTE) (eg, total hip replacement)

Innohep® in Renal Insufficiency Study (IRIS)¹

The IRIS study was a multi-centre European study designed to compare the safety profile of Innohep® with UFH in the initial treatment of acute DVT in patients greater than 70 years of age with impaired renal function (i.e. patients > 70 years with estimated creatinine clearance of < 30ml/min or patients > 75 years with estimated creatinine clearance of < 60 ml/min). In the study, patients were randomised to treatment with either Innohep® (fixed dose of 175IU/kg subcutaneous injection once daily) or UFH (IV bolus followed by subcutaneous injections twice daily) for at least 5 days followed by oral anti-coagulant treatment for at least 90+/-5 days.

Interim analysis

During the planned interim analysis, an increase in all-cause mortality in the Innohep® arm compared to the UFH arm was identified, which led to a premature discontinuation of the study. At the time the study was stopped, 350 patients had completed 90 days of follow-up. Of these, 23 of the 176 (13%) patients in the Innohep® group versus 9 of the 174 (5%) patients in the UFH group had died.¹

Following the termination of the study, although patient recruitment was stopped, all patients who were previously enrolled and had completed the subcutaneous period with Innohep® or UFH treatment continued the study according to the protocol. When the total enrolled population had been followed up to day 90, there were a total of 537 patients who were evaluated. Of these 537 patients, 11.2% patients in the Innohep® group (n=269) and 6.3% patients in the UFH group (n=268) had

died ($p=0.049$).^{2,3} The difference in mortality was not due to recurrent VTE or bleeding. Most of the difference in mortality was in those aged 90 years and above (9.4% in the UFH group vs. 30.8% in the Innohep® group). Below 90 years, the mortality rates were 5.9% vs. 7.8%, respectively.³

A review of risk factors suggested an imbalance at randomisation with a higher percentage in the Innohep® group having risk factors for death. When adjusted for baseline characteristics using multiple regression analysis, the relative risk of dying in the Innohep® group versus the UFH group was found not to be statistically significant. In addition, four parameters were found to be correlated to mortality, namely ongoing malignancy, infectious disease, age > 90 years and cardiac insufficiency. All of these four identified risk factors for death were found to be more common in the Innohep® group than the UFH group.³

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

In response to the interim finding of the IRIS study, showing an increase in all-cause mortality in patients receiving Innohep®, the US FDA posted a public communication highlighting these results on their website.²

Although it was understood that FDA is still finalising their safety review of Innohep® and had not concluded on the association between Innohep® and mortality, the US product insert was updated to describe the interim study results in the labelling of Innohep®, suggesting that Innohep® increases the risk of death for elderly patients (i.e. 70 years of age and older) with renal insufficiency. A Dear Healthcare Professional Letter (DHCPL) was also issued to the healthcare professionals to inform them of the interim results of the IRIS study as well as the package insert update.³

Local Situation

To date, HSA has not received any local ADR reports related to the use of Innohep®. HSA is working with the company to strengthen the local package insert for Innohep® to caution on the use of Innohep® in patients with renal impairment and to monitor patients for anti-factor Xa activity.

Healthcare professionals are advised to take into consideration the above safety update when prescribing Innohep® to their patients and to report all suspected adverse reactions associated with Innohep® to the Vigilance Branch of HSA.

References

1. FDA Communication about an ongoing safety review of Innohep® <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafety/InformationforPatientsandProviders/DrugSafety/InformationforHealthcareProfessionals/ucm136254.htm>
2. Celgene – DHCPL on important Innohep® safety information <http://www.fda.gov/downloads/Safety/MedWatchSafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm128135.pdf>
3. Leizorovicz A. Tinzaparin Compared to Unfractionated Heparin for Initial Treatment of Deep Vein Thrombosis in Very Elderly Patients with Renal Insufficiency: the IRIS Trial. *Blood* 2008; 112(11): 166

Summary of safety advisories issued by HSA and pharmaceutical companies

Summary of Dear Healthcare Professional Letters issued by HSA and/or pharmaceutical companies from November 2008 to November 2009. For details, please log on to <http://www.hpp.moh.gov.sg> using your professional board register number or Singpass.

- 19 Dec 2008 – Reports of Pure Red Cell Aplasia in patients treated with CellCept® (mycophenolate mofetil) [Roche]
- 1 Jan 2009 – Zelmac® tablet 6mg (tegaserod maleate) – Safety-related Package Insert Update
- 26 Feb 2009 – Sales of Raptiva® (Efalizumab) suspended
- 12 Mar 2009 – Product Notification on Desferrioxamine mesylate for injection [Hospira]
- 15 Apr 2009 – Information on the association of erlotinib (Tarceva®) with gastrointestinal perforation, Stevens-Johnson syndrome, and corneal perforation or ulceration [Roche]
- 31 Jul 2009 – Update on neuropsychiatric adverse events suspected to be associated with oseltamivir (Tamiflu®)
- 7 Sep 2009 – Compliance to the safety monitoring protocols of the 'RevAssure Program' of lenalidomide (Revlimid®), an analogue of thalidomide
- 14 Oct 2009 – Zanamivir (Relenza®) inhalation powder must not be nebulised [GSK]
- 4 Nov 2009 – Monitoring the safety profile of Influenza A/H1N1 (2009) vaccines

Package insert amendments reflecting safety issues

HSA has approved the following package insert changes due to safety updates from May 2009 to September 2009. 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/safetyinfo_and_recalls. Please also note that there might be some lag time in the availability of the package insert which reflects the latest change(s)

1. Amlodipine, valsartan (Exforge®, Novartis) Undesirable effects: Patients with severe obstructive coronary artery disease, rarely developed increased frequency, duration or severity of angina or acute myocardial infarction on starting amlodipine therapy or at time of dosage increase. Arrhythmia (including ventricular tachycardia & atrial fibrillation) reported with calcium channel blocker therapy. Neutropenia observed in 1.9% of patients treated with valsartan vs 1.6% of patients treated with ACEI.

2. Amoxicillin, clavulanic acid (Augmentin ES®, GSK) Warning: Abnormal prolongation of prothrombin time (PT) reported rarely in patients receiving Augmentin® & oral anticoagulants. Interactions: combined oral contraceptives. Rare cases of increased international normalised ratio (INR) in patients maintained on acenocoumarol or warfarin & amoxicillin. Monitor PT or INR when adding or withdrawing Augmentin ES®. New ADR: Black hairy tongue.

3. Amphotericin B (Ambisome®, Gilead Sciences) New ADR: Bronchospasm.

Amphotericin B (Fungizone® IV, Bristol-Myers) Warning: Should not be given at doses >1.5mg/kg. Exercise caution to prevent inadvertent overdose, which can result in potentially fatal cardiac or cardiorespiratory arrest. New ADRs: Skin exfoliation, TEN, Stevens Johnson Syndrome, nephrogenic diabetes insipidus.

4. Atovaquone, proguanil (Malarone®, GSK) Interaction: Proguanil may potentiate the anticoagulant effect of warfarin & other coumarin based anticoagulants. Caution advised when initiating or withdrawing malaria prophylaxis or treatment with atovaquone-proguanil in patients on continuous treatment with coumarin based anticoagulants. New ADRs: SJS, erythema multiforme, vasculitis, cholestasis.

5. Carbidopa, levodopa (Sinemet CR®, MSD) Precautions: Patients with Parkinson's disease have higher risk (2- to approximately 6-fold higher) of developing melanoma than the general population. Periodic skin examinations should be performed by specialists (eg, dermatologists). Pathological gambling, hypersexuality & increased libido reported in patients treated with dopamine agonists for Parkinson's disease. Pathological (compulsive) gambling reported rarely in patients treated with levodopa &/or dopamine receptor agonists.

6. Carbimazole (Carbimazole®, Sunward) Warnings: Fatal cases of agranulocytosis reported & early treatment is essential. Discontinue drug following onset of signs & symptoms of hepatic disorder & perform liver function tests immediately. Use with caution in patients with mild-moderate hepatic insufficiency, intrathoracic goitre. Stop treatment temporarily at time of administration of radio-iodine (to avoid thyroid crisis). Use in non-pregnant women of childbearing potential should be based on individual risk/benefit assessment. Risk of cross-allergy between carbimazole, active metabolite thiamazole (methimazole) & propylthiouracil. Adverse effects: Hepatic disorders, including abnormal liver function tests, cholestatic hepatitis, cholestatic jaundice & most commonly jaundice.

7. Disodium pamidronate (Pamisol® inj, Hospira) Contraindicated in pregnancy & breastfeeding. Precautions: Ensure appropriate hydration in patients before administration, esp. in patients receiving diuretic therapy. Disodium pamidronate associated with renal toxicity - renal deterioration, progression to renal failure & dialysis reported in patients after initial dose or single dose. Deterioration of renal function (including renal failure) also reported following long-term treatment in patients with multiple myeloma; risk in these patients increases with concomitant use with thalidomide. Should not be administered to patients with severe renal impairment (CrCl <30 mL/min) except in life-threatening tumour-induced hypercalcaemia. Osteonecrosis of the jaw (ONJ) reported predominantly in cancer patients treated with disodium pamidronate. Most of these also received chemotherapy & corticosteroids & had signs of local infection including osteomyelitis. For patients who develop ONJ while on therapy, dental surgery may exacerbate condition. Risk factors for ONJ: diagnosis of cancer, concomitant chemotherapy, radiotherapy, corticosteroids & co-morbid conditions (e.g. anaemia, coagulopathies, infection, pre-existing oral disease). Severe & occasionally incapacitating but reversible bone, joint, &/or muscle pain reported infrequently in patients taking

biphosphonates. Interactions: potentially nephrotoxic drugs. New ADR: Focal segmental glomerulosclerosis, including the collapsing variant nephrotic syndrome.

8. Enalapril (Renitec®, MSD) Precautions: Hyperkalaemia leading to serious & sometimes fatal, arrhythmias. Very rarely, fatalities reported due to angioedema associated with laryngeal oedema or tongue oedema. Patients with involvement of the tongue, glottis or larynx are likely to experience airway obstruction, esp. those with a history of airway surgery. Interactions: ACE inhibitors, injectable gold (sodium aurothiomalate), antidiabetic medicines, NSAIDs. Diabetic patients treated with oral antidiabetic agents or insulin, should be closely monitored for hypoglycaemia, esp. during 1st month of treatment with an ACE inhibitor. In renally impaired patients treated with NSAIDs or selective COX-2 inhibitors, co-administration of angiotensin II receptor antagonists or ACE inhibitors may result in renal function deterioration. New ADR: SIADH, hypoglycaemia, intestinal angioedema.

9. Epoetin alfa (Eprex®, J&J) Special warnings: Antibody-mediated pure red cell aplasia very rarely reported after months to years of SC epoetin treatment in chronic renal failure patients. Cases also rarely reported in patients with hepatitis C treated with interferon & ribavirin, when erythropoiesis-stimulating agents (ESAs) are used concomitantly. ESAs are not approved in the management of anaemia associated with hepatitis C.

10. Ezetimibe (Ezetrol®, Schering-Plough) New ADR: Erythema multiforme.

Ezetimibe, simvastatin (Vytorin®, MSD) New ADRs reported post-market: Erythema multiforme, memory impairment, insomnia.

11. Fluoxetine (Prozac®, Eli Lilly) Precautions: Increased risk of suicidal ideation &/or suicidal behaviours in paediatric & young adult (<25 years of age) patients compared to placebo. Interaction: drugs with serotonergic activity (e.g. SNRIs, SSRIs, triptans or tramadol). New ADRs: Palpitations, oesophageal pain, dysgeusia, abnormal feeling/thinking, jittery feeling, anaphylactic reaction, contusion, muscle twitching, balance disorder, buccoglossal syndrome, disturbance in attention, dyskinesia, bruxism, depersonalisation, euphoric/elevated mood, decreased libido, sleep disorder, dysuria, erectile dysfunction, gynaecological bleeding (e.g. dysfunctional uterine bleeding, menorrhagia), hyperhidrosis, increased tendency to bruise, exfoliative rash, epistaxis in children.

12. Hepatitis B vaccine (Engerix-B®, GSK) Special warning: Potential risk of apnoea & need for respiratory monitoring for 48-72h when administering primary immunization series to very premature infants (born = 28 weeks of gestation) & esp. for those with a previous history of respiratory immaturity. New ADRs: Lost appetite, irritability, drowsiness, hypoaesthesia, asthenia, muscular weakness, lichen planus.

13. Ketotifen (Zaditen®, Novartis) Special warnings: Convulsions reported very rarely during therapy. Use with caution in patients with history of epilepsy as Zaditen® may lower seizure threshold. Caution in diabetic patients due to carbohydrate contents. Interaction: CNS depressants. New ADRs: Cystitis, erythema multiforme, Stevens-Johnson syndrome, severe skin reaction, irritability, insomnia, nervousness, hepatitis, increase in liver enzymes. Excitation, irritability, insomnia, & nervousness, observed esp. in children.

14. Levodopa, carbidopa, entacapone (Stalevo®, Novartis) Special warning: For patients who experience progressive anorexia, asthenia & weight decrease within a relatively short period of time, general medical evaluation including liver function should be considered. New ADRs: Hepatitis with mainly cholestatic features; skin, hair, beard & nail discolourations.

15. Lisinopril (Lisdene®, Sandoz) Contraindication: Hereditary or idiopathic angioedema.

Interactions: diuretics, potassium supplements or potassium-containing salt substitutes, lithium (esp with concomitant use of thiazide diuretics), NSAIDs, injectable gold (sodium aurothiomalate), antihypertensive agents, GTN & other nitrates, vasodilators, anaesthetic medicinal products, TCAs & antipsychotics, sympathomimetics, antidiabetic medicines (insulins, oral hypoglycaemic agents). New ADRs: haemoglobin decrease, haematocrit decrease, bone marrow depression, anaemia, thrombocytopenia, leucopenia, neutropenia, agranulocytosis, haemolytic anaemia, lymphadenopathy, autoimmune disease, hypoglycaemia, mental confusion, vertigo, paraesthesia, bronchospasm, allergic alveolitis/eosinophilic pneumonia, intestinal angioedema, hepatocellular or cholestatic hepatitis, hypersensitivity/angioneurotic oedema, pemphigus, toxic epidermal necrolysis, Stevens Johnson syndrome, erythema multiforme, cutaneous pseudolymphoma, renal dysfunction, uraemia, oliguria/anuria, increases in blood urea, increases in serum creatinine, increases in liver enzymes, hyperkalaemia, myocardial infarction or cerebrovascular accident, possibly 2° to excessive hypotension in high risk patients, a symptom complex which may include one or more of the following: fever, vasculitis,

myalgia, arthralgia/arthritis, a positive antinuclear antibodies (ANA), elevated red blood cell sedimentation rate (ESR), eosinophilia & leucocytosis, rash, photosensitivity or other dermatological manifestations.

16. Medroxyprogesterone (Depo-provera® & Provera®, Pfizer) Special warning: Medroxyprogesterone acetate (MPA) not recommended in patient with history of venous thromboembolism (VTE). Discontinuation of MPA recommended in patients who develop VTE while undergoing therapy with MPA.

17. Mesalazine (Salofalk®, IDS) Special warnings: Discontinue treatment immediately in the event of acute symptoms e.g. convulsions, cramps, acute abdominal pain, fever, severe headache or rash. Salofalk(R) 4g/60ml enemas: Not to be used in children <40 kg. New ADRs: Peripheral neuropathy, oligospermia.

18. Paricalcitol (Zemlar® inj, Abbott) Interaction: Study with ketoconazole & paricalcitol capsule demonstrated ketoconazole approximately doubled paricalcitol AUC. Care should be taken while dosing paricalcitol with ketoconazole & other strong P450 3A inhibitors. New ADRs: Angioedema, laryngeal oedema.

19. Phenytoin (Dilantin®, Pfizer) Special warnings: Anticonvulsant Hypersensitivity Syndrome (AHS)- a rare drug induced, multiorgan syndrome which is potentially fatal & occurs in some patients taking anticonvulsant medication. More severe in previously sensitized individuals. Characterised by fever, rash, lymphadenopathy, & other multiorgan pathologies, often hepatic. Interval between 1st drug exposure & symptoms is usually 2-4 weeks but has been reported in individuals receiving anticonvulsants for ≥3 months. Risk factors: black patients, those with family history of or who have experienced this syndrome in the past & immuno-suppressed patients. Limited evidence suggests HLA-B*1502 may be risk factor for development of SJS/TEN in patients of Asian ancestry taking drugs associated with SJS/TEN, including phenytoin. Avoid use of drugs associated with SJS/TEN, including phenytoin, in HLA-B*1502 +ve patients. Phenytoin & other anticonvulsants may induce CYP450 enzyme which affects bone mineral metabolism leading to Vitamin D deficiency & increased risk of osteomalacia, bone fractures, osteoporosis, hypocalcaemia, & hypophosphatemia in chronically treated (>10 years) epileptic patients. Interactions: nelfinavir, ciprofloxacin.

20. Raltitrexed (Tomudex®, Hospira) Precaution: Potential for accumulation of raltitrexed in elderly patients due to decline in renal function & reduced plasma clearance. Monitor ADRs esp. signs of GI toxicity (diarrhoea or mucositis) & myelosuppression (neutropenia, thrombocytopenia & infection). Reduce &/or delay dose as appropriate. New ADRs: Oral moniliasis, stomatitis, increased creatinine, hypokalaemia, myalgia, depression, insomnia, paraesthesia, increased cough, dyspnoea, epistaxis, hiccup, pharyngitis, rhinitis, herpes simplex, urinary tract infection, enlarged abdomen, mucous membrane disorder.

21. Ranibizumab (Lucentis® soln for inj, Novartis) New ADR: Stroke. Potential risk of arterial thromboembolic events following intravitreal use of vascular endothelial growth factor (VEGF) inhibitors. Higher stroke rate observed in patients with neovascular (wet) age-related macular degeneration treated with 0.5mg intravitreal ranibizumab compared to 0.3mg intravitreal ranibizumab (1.2% vs 0.7% respectively). Stroke rates may be greater in patients with known risk factors for stroke.

22. Salmeterol, fluticasone (Seretide®, GSK) Warning: Study showed concomitant use of systemic ketoconazole increases exposure to Serevent® and may lead to prolongation in QTc interval. Caution during coadministration of strong CYP3A4 inhibitors (e.g. ketoconazole) with Serevent®. New ADR: Contusions.

23. Telbivudine (Sebivo®, Novartis) New ADRs: Dysgeusia, hypoaesthesia, paraesthesia, sciatica, increased blood amylase, increased blood lipase, increased blood ALT, increased AST. Severe acute exacerbations of hepatitis reported in patients who have discontinued anti-hepatitis B therapy. Rhabdomyolysis reported very rarely post-market.

24. Temozolomide (TemodalR®, Schering-Plough) Contraindicated in breast feeding. Warnings/precautions: Effect on testes in animals suggest strong possibility for additional reproductive effects including infertility & possibly delayed offspring effects resulting in genetic damage to germ cells. Multiple cycles studies indicated testicular toxicity, effective contraception should be used by both male & female patients who are taking Temodal®. New ADRs: TEN, Stevens Johnson syndrome, interstitial pneumonitis/pneumonitis.

25. Tiotropium (Spiriva®, Boehringer Ingelheim) New ADRs: Dehydration, insomnia, laryngitis, pharyngitis, sinusitis, stomatitis, gingivitis, glossitis, skin infection, skin ulcer, dry skin, joint swelling.

26. Vildagliptin (Galvus®, Novartis) New ADRs: Arthralgia, upper respiratory tract infection, nasopharyngitis, urticaria. Not recommended in patients with moderate or severe renal impairment or End Stage Renal Disease on haemodialysis.

Local experience with oseltamivir (Tamiflu®)

Update on neuropsychiatric events associated with oseltamivir

HSA would like to update healthcare professionals on the local ADR reports associated with oseltamivir (Tamiflu®, Roche) since the issuance of the Dear Healthcare Professional Letter on 31 July 2009 on the same subject (please log on to <http://www.hpp.moh.gov.sg> for details of letter).

Background

HSA had earlier published a report on oseltamivir and neuropsychiatric events in its December 2006 Vol. 8 No. 3 issue of the HSA ADR News Bulletin. In the article, it was reported that the majority of the cases originated from Japan. They were primarily among paediatric patients (67%) with an age range of 1.5 to 17 years old. Most of the adverse events occurred during the first day of oseltamivir use (1 to 2 doses).

As a result of these findings, the local prescribing information of Tamiflu® was updated to include warnings on the potential of the occurrence of neuropsychiatric adverse events. It cautioned that patients with influenza, particularly children may be at an increased risk of self injury and confusion shortly after taking Tamiflu® and should be closely monitored for signs of unusual behaviour.

Since the start of the Influenza A/H1N1 (2009) influenza pandemic, there has been a sharp increase in the usage of oseltamivir. A corresponding increase in the number of adverse drug reactions (ADR) associated with oseltamivir, notably neuropsychiatric events was reported. On 31 July 2009, HSA issued a Dear Healthcare Professional Letter (DHCPL) to remind healthcare professionals to closely monitor patients prescribed Tamiflu® for the development of neuropsychiatric events as these events, although rare, are often unpredictable and potentially fatal.



Recent local reports of central nervous system (CNS) disorders

As of 1 October 2009, HSA's Vigilance Branch received a total of 42 ADR reports suspected to be associated with Tamiflu® (36 were received after 1 July 2009). Out of the 42 reports, 23 were CNS related. They include the following ADR terms:

agitation (1),	dreaming	involuntary	simple partial
anxiety (1),	abnormal(1),	movement oral (1),	seizures (1),
cognitive function	drowsiness (1),	lethargy (1),	sleep walking (1),
abnormal (1),	giddiness (1),	mental state	staring (2),
confusion (2),	hallucination (2),	abnormal (1),	status
crying abnormal (1),	hallucination	nightmares (3),	epilepticus (1),
delirium (3),	auditory (1),	nodding of	suicidal
disorientation (2),	headache (1),	head (1),	tendency (2)
disturbance in social	hypoactivity (2),	panic reaction (2),	suicide (1).
behaviour (3),	insomnia (1),	psychotic state (1),	

*An ADR report may describe more than one ADR term.

Majority of these patients were young patients (74%) (17 patients were ≤17 years and six were ≥18 years). 15 (65%) were males and eight (35%) were females.

The remaining 19 ADR reports received include hepatitis (1); G6PD hemolytic anaemia (1); epistaxis in an elderly patient (1); severe stomach pain & vomiting (2); aggravation of diabetes in a diabetic patient (1); increase in INR (1) and non serious reports of rash, allergy, periorbital swelling, nausea (12).

Many events such as convulsions, delirium and depressed levels of consciousness may be possible complications of viral encephalitis secondary to influenza. Influenza infection itself can also be associated with a variety of neurologic and behavioural symptoms such as abnormal behaviour, hallucinations, agitation, anxiety and nightmares. It therefore remains unclear whether these neuropsychiatric events were the outcomes of the direct adverse effect of the drug, genetic differences in metabolic handling of oseltamivir, unusual manifestation of the underlying infection or a combination of any of these possible factors.

Conclusion

HSA will continue to closely monitor this emerging safety concern and update our healthcare professionals. All healthcare professionals are encouraged to report all serious side effects including neuropsychiatric adverse events suspected to be associated with oseltamivir to the Vigilance Branch of HSA.

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