HSA would like to update healthcare professionals on the trend of lymphadenitis and injection-site reactions associated with the Bacillus Calmette-Guérin (BCG) vaccine SSI® (DKSH Singapore Pte Ltd). Since our last update in December 2011 on the increase in local cases of suppurative lymphadenitis, the incidence of lymphadenitis has been on the downturn.

In Singapore, BCG vaccine is routinely administered to all neonates at birth as part of the National Childhood Immunisation Schedule (NCIS). The BCG vaccine SSI® containing an attenuated strain of Mycobacterium bovis (Danish strain 1331) has been the only BCG vaccine registered in Singapore since June 2003.

Reports of lymphadenitis

An increase in local cases of BCG-associated suppurative lymphadenitis was first observed in 2011, based on the vaccine adverse event (VAE) reports obtained from the active surveillance sentinel site at KK Women’s and Children’s Hospital (KKH) and spontaneous reporting by healthcare professionals. As of end August 2014, the estimated incidences of suppurative lymphadenitis and non-suppurative lymphadenitis for the 2009 to 2013 vaccinated cohorts ranged from 0.48 to 3.18 per 1,000 vaccinees and 0.10 to 0.79 per 1,000 vaccinees, respectively (Figure 1). Although the upper bound of this estimate was higher than that in the package insert, it still remained within the values that had been reported globally for this brand of vaccine. Following a peak in cases reported in the 2011 vaccinated cohort, the incidences of suppurative and non-suppurative lymphadenitis have since returned to baseline levels.

Figure 1. Incidence of lymphadenitis for the 2009 to 2013 vaccinated cohorts

Suppurative lymphadenitis is defined as the presence of fluctuation on palpation or pus on aspiration, the presence of a sinus, or large lymph nodes adherent to skin with caseous lesions on excision. The estimates for non-suppurative cases are likely to be underestimates as these cases are usually not reported to HSA given that it is a common and expected reaction post-BCG vaccination.

An investigation into the possible causes behind the higher incidence of suppurative lymphadenitis involving the 2011 vaccinated cohort was conducted by HSA. Possible causes such as issues related to vaccine quality, vaccine administration practice or techniques and host characteristics were evaluated in detail. HSA’s investigation revealed that the issue may be batch-related as a result of vaccine manufacturing issues, after ruling out vaccine administration-related and host-related factors.

Further investigation conducted by the manufacturer identified the possible cause to be due to a period of manufacturing with a slower growth of the bacilli. One postulation could be that the higher level of bacterial by-products as a result of the slower growth of the bacilli may have triggered lymphadenitis in some patients, although the manufacturer was unable to confirm this. The trending of the incidence of suppurative lymphadenitis of all batches administered from 2009 to 2013 in Singapore appeared to be consistent with the manufacturer’s investigation, with lower incidences of suppurative lymphadenitis (0.1–1 per 1,000 vaccinees) reported in batches manufactured before and after the period of the slower growth issue. Rectifications made by the manufacturer had seen the incidence of suppurative lymphadenitis returning to baseline levels. Further details may be found in the joint publication by HSA and KKH.
Local situation and HSA’s advisory

HSA has not received any local adverse reaction reports of TMA and nephrotic syndrome associated with the use of interferon beta products. The local package inserts of Rebif® and Betaferon® have been strengthened to include warnings on the risk of these safety concerns.

Healthcare professionals are advised to monitor and consider the possibility of TMA and nephrotic syndrome in patients treated with interferon beta products, if signs and symptoms consistent with these diagnoses are identified.

References
2 http://www.mhra.gov.uk/Safetyinformation/DraftSafetyUpdate/ CON462300

Overseas reports of hepatic injury associated with Radix Polygoni Multiflori

HSA would like to inform healthcare professionals that the China Food and Drug Administration (CFDA) has recently issued an alert on the possible risk of hepatotoxicity associated with oral intake of Radix Polygoni Multiflori (also known as Heshouwu or 何首乌). Heshouwu is obtained from the dried root tuber of Polygonum multiflorum Thunb, and its indications may include premature greying of hair, high blood lipid levels and weakness of the knees and lower back. Most of the reported hepatic injuries were generally considered mild or moderate in nature and were reversible upon cessation of the suspected product; however, there were cases of severe liver injuries. Other risk factors of hepatotoxicity include overdosing, prolonged usage, medical history of prior liver injury and the concomitant use of other hepatotoxic drugs.

HSA has received two adverse reaction reports of hepatitis suspected to be associated with two health products containing Heshouwu in June 2010 and July 2013. The first report involved a 51-year-old female who took the product for about a month before developing the adverse reaction. In the second report, a 46-year-old male who took the product for five months was complicated by the fact that the patients were also taking other complementary medicines.

While the review by HSA on this issue is ongoing, healthcare professionals are advised to be vigilant to the possibility of hepatotoxicity associated with Heshouwu. 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 reactions reported could be related to such products. Healthcare professionals are also encouraged to report any adverse reactions suspected to be associated with the use of Heshouwu to the Vigilance and Compliance Branch of HSA.

References
1 Pharmacopoeia of the People’s Republic of China 2010
(English Edition)
2 http://www.sfda.gov.cn/WS01/CL0078/102903.html
HSA would like to remind healthcare professionals about the risk of cardiovascular, neurological and psychiatric adverse effects that are known to be associated with the use of bromocriptine. These rare but potentially serious or fatal adverse effects were highlighted by the European Medicines Agency’s (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) in its recently completed safety review, which advised against the routine use of bromocriptine-containing medicines for the prevention or suppression of lactation, as well as for relieving symptoms of pain or swelling of the breasts postpartum.1

Bromocriptine is a dopamine agonist that has been authorised across Europe for use in the prevention and suppression of lactation postpartum. However, locally, it is not licensed for such use and is not recommended for the routine prevention or suppression of puerperal breast engorgement.

In Singapore, bromocriptine (Parlodel®, Novartis (Singapore) Pte Ltd) has been registered since May 1988 for the treatment of Parkinson’s disease, prolactinomas, acromegaly, hyperprolactinaemia in men, as well as menstrual cycle disorders and female infertility. There are also several generic brands of bromocriptine registered locally, namely Apo-bromocriptine® (Pharmaforte Singapore Pte Ltd), Brameston® (Goldplus Universal Pte Ltd) and Bromocriptin-Richter® (Pharmline Marketing Pte Ltd).

**EMA’s review of bromocriptine-containing medicines**

In September 2013, EMA’s PRAC initiated a safety review of bromocriptine-containing medicines for the prevention or suppression of lactation postpartum.2 This review was requested by the French medicines agency (ANSM) following concerns of rare but potentially serious or fatal adverse effects associated with the use of bromocriptine. These included cardiovascular diseases (e.g., heart attack and stroke), neurological effects (e.g., fits) and psychiatric effects (e.g., hallucinations and manic episodes) that were observed from the French pharmacovigilance database and global safety databases of companies for the period 1985 to 2012. ANSM considered that the risk of these events was not acceptable in view of the availability of alternative means of management, and that breast milk production will naturally cease if the mother stops breastfeeding her infant.

In July 2014, the PRAC completed its review,1 taking into consideration available data from post-marketing spontaneous case reports, clinical trials and published literature relating to cardiovascular, neurological and psychiatric risks following treatment with bromocriptine-containing medicines in postpartum lactation inhibition. The outcome of the review concluded that although bromocriptine was effective for the prevention or suppression of lactation postpartum, an association between bromocriptine treatment and adverse events such as heart attack, stroke, fits, and psychiatric disorders could not be ruled out. PRAC recommended that bromocriptine (up to 2.5mg) should only be used in the presence of compelling medical reasons for stopping lactation. Bromocriptine should not be used routinely for prevention or suppression of lactation, nor to relieve symptoms of pain or swelling of the breasts postpartum.

In addition, women at high risk of serious adverse effects, such as those with severe psychiatric disorders and those with disorders that increase blood pressure, should not be treated with bromocriptine. Blood pressure monitoring is recommended in patients using bromocriptine to detect early signs of problems that may warrant discontinuation of the treatment.

**Local situation and HSA’s advisory**

To date, HSA has received two non-serious adverse reaction reports associated with the use of bromocriptine for the suppression of lactation (off-label use). The adverse reactions reported included rash, facial oedema and peripheral oedema.

HSA would like to highlight to healthcare professionals that bromocriptine-containing products are not licensed locally for the prevention and suppression of lactation postpartum. Bromocriptine-containing products are also not recommended for use in the routine prevention or suppression of puerperal breast engorgement as such symptoms can usually be treated with simple analgesics and managed by non-pharmacological interventions such as firm breast support or ice application.

There are existing warnings regarding cardiovascular, neurological and psychiatric concerns in the local package inserts of bromocriptine-containing products, including the need for periodic blood pressure monitoring. Healthcare professionals are advised to take into consideration these labelled warnings when prescribing bromocriptine to patients. They should also be aware of the above safety review by PRAC and its recommendations on the use of bromocriptine for suppression of lactation as authorised in Europe.

**References**

HSA’s new website (www.hsa.gov.sg), launched in July 2014, was conceptualised with our end-users in mind. The planning of the contents and overall design took into account the browsing habits of visitors, stakeholders’ feedback, and the findings of a healthcare professional survey.

Users can now look forward to a more user-friendly website with enhanced features that enable quicker access to information and easier navigation, particularly for frequently visited services.

We would like to highlight five features that have been enhanced to facilitate convenient access to information.

Please feel free to provide your comments or feedback via the link to the online form at the top of the main page, or e-mail us at HSA_Info@hsa.gov.sg. We would also like to take this opportunity to thank all healthcare professionals for their participation in the survey.
Recently, it came to HSA’s attention that some digital and infra-red thermometers, classified as medium risk Class B devices, that are being supplied and sold in Singapore have not been registered with HSA.

Under the current regulations, these thermometers must be registered with HSA to ensure that they are manufactured at sites compliant with appropriate quality systems (e.g., ISO 13485) and have been validated to appropriate international standards (e.g., ISO 80601-2-56, EN 12470, ASTM E1965-98) or equivalent to meet essential requirements for safety and performance as applicable to the device.

In addition, the dealers (i.e. importers and wholesalers) supplying these thermometers must also be licensed by HSA. This is to ensure that they implement and maintain the appropriate quality practices to ensure the adequate control of documents and records, inspection of inventory, proper handling and storage of devices, shelf-life monitoring, as well as segregation of expired stocks. Dealers are required to register their digital and infra-red thermometers by 1 May 2015 or enforcement actions may be taken against them.

Advice for healthcare professionals and institutions

Healthcare professionals or institutions using unregistered thermometers are advised to switch to registered thermometers. They are also strongly advised to purchase registered thermometers from licensed dealers. Healthcare professionals and the relevant departments of healthcare institutions are encouraged to refer to the Singapore Medical Device Register (SMDR) at http://www.hsa.gov.sg to check if their thermometers are registered with HSA.

Healthcare professionals can contact the Medical Device Branch (Thermometer Advisory) at 6304 5461 or 6866 1078 should they need to clarify on the registration status and the licensing and registration processes for thermometers.

4 Safety information glossary
Provides quick access to safety alerts, product recalls and other safety-related information for health products, segregated by active ingredient/product name.

3 New e-services page
A consolidated e-services page with quick links for reporting ADRs, or to search for registered medicinal products, medical devices or clinical trial applications.

5 New look on mobile web browser platform
Development of a new mobile web version for convenient browsing of the HSA website on your smartphone or tablet.

Advisory note on use of registered thermometers

Recently, it came to HSA’s attention that some digital and infra-red thermometers, classified as medium risk Class B devices, that are being supplied and sold in Singapore have not been registered with HSA.

Under the current regulations, these thermometers must be registered with HSA to ensure that they are manufactured at sites compliant with appropriate quality systems (e.g., ISO 13485) and have been validated to appropriate international standards (e.g., ISO 80601-2-56, EN 12470, ASTM E1965-98) or equivalent to meet essential requirements for safety and performance as applicable to the device.

In addition, the dealers (i.e. importers and wholesalers) supplying these thermometers must also be licensed by HSA. This is to ensure that they implement and maintain the appropriate quality practices to ensure the adequate control of documents and records, inspection of inventory, proper handling and storage of devices, shelf-life monitoring, as well as segregation of expired stocks. Dealers are required to register their digital and infra-red thermometers by 1 May 2015 or enforcement actions may be taken against them.

Advice for healthcare professionals and institutions

Healthcare professionals or institutions using unregistered thermometers are advised to switch to registered thermometers. They are also strongly advised to purchase registered thermometers from licensed dealers. Healthcare professionals and the relevant departments of healthcare institutions are encouraged to refer to the Singapore Medical Device Register (SMDR) at http://www.hsa.gov.sg to check if their thermometers are registered with HSA.

Healthcare professionals can contact the Medical Device Branch (Thermometer Advisory) at 6304 5461 or 6866 1078 should they need to clarify on the registration status and the licensing and registration processes for thermometers.
Adulteration of three health products with undeclared chemical ingredients, including sibutramine

Three adulterated health products were recently detected by HSA through its post-market surveillance programme, as well as feedback from a member of the public and a Traditional Chinese Medicine (TCM) practitioner. The products were sold as traditional herbal treatments or health supplements and carried claims of being 100% natural or of herbal origin, but were tested by HSA’s Pharmaceutical Laboratory to contain undeclared chemicals such as western medicinal ingredients and their analogues.

Investigations revealed that these adulterated products were obtained from different sources, including a local retail shop, the internet, or an acquaintance. HSA had issued press releases in October and November this year to alert the public against taking the following products:

1. ‘AMACE for him’

‘AMACE for him’ was sold by a local retail shop at Balestier Plaza as a health supplement, and labelled to contain only natural ingredients such as lingzhi, ginseng, cordyceps and wolfberry. The product was marketed as an energy and immune booster, for the promotion of blood circulation and for sexual enhancement. Tests on the product found that it contained N-cyclopentyl nortadalafil, an analogue of tadalafil. The local retailer was instructed by HSA to initiate a recall of the product.

2. ‘Li Da DAIDAIHUA Weight Loss Capsule’

‘Li Da DAIDAIHUA Weight Loss Capsule’, which was labelled to be 100% herbal with botanical ingredients such as Daidaihua, Indian lotus leaf and Cassia seed, was sold through the internet as a food supplement for weight management. A vigilant member of the public alerted HSA to the sale of this product. Laboratory tests identified the presence of sibutramine and its analogue, benzyl sibutramine, in the product. Sibutramine has been withdrawn from the Singapore market and other countries since 2010 due to an increased risk of serious cardiovascular events which outweighed its modest efficacy in weight loss. The safety profile of the sibutramine analogue is unknown.

3. ‘Du Zhong Jin Gu Wan’

‘Du Zhong Jin Gu Wan’ was purchased by a woman in her 70s from an acquaintance for the treatment of her arthritis. The product was sold as a herbal preparation and labelled to contain natural ingredients including cordyceps. The capsules were poorly packaged in a transparent bag, accompanied by a leaflet titled ‘杜仲筋骨丸’. An astute TCM practitioner became concerned about the product after his patient reported immediate pain relief from its use. Laboratory tests on the product identified the presence of three adulterants, namely chlorpheniramine, dexamethasone and diclofenac.

HSA’s advisory

Given the increasing trend of consumers turning to the use of alternative treatments such as herbal and traditional preparations, healthcare professionals are encouraged to ask their patients about the use of such health products when taking their medication history. This information may be useful for the differential diagnosis of adverse events experienced by their patients, which may be attributed to the adulterant(s) in the health products that were consumed.
As the year draws to a close, we would like to thank all healthcare professionals for your active participation in the reporting of adverse events suspected to be associated with health products. Through your constant vigilance, we have managed to detect important safety signals and uncover several cases of adulterated complementary health products.

We recognise the importance of informing healthcare professionals on health product safety information in a timely manner so that you can make better informed decisions on the use of the affected health product. In addition to the HSA ADR News bulletin which most healthcare professionals would be familiar with, other safety-related information which are available on our website include safety alerts, product recalls, press releases, and abstracts of Dear Healthcare Professional Letters. We hope that the revamped HSA website will facilitate convenient access to such information.

The editorial team of the HSA ADR News bulletin wishes all our readers a brand New Year of opportunities, joy and good health!

Editor-in-chief
Chan Cheng Leng

List of Dear Healthcare Professional Letters (DHCPL) issued by HSA, pharmaceutical and medical device companies between 26 July and 28 November 2014

For details, please log on to MOHAalert via your professional board’s website.

Therapeutic products

30 Jul 2014 Reminyl® (galantamine hydrobromide): New warning on serious skin reactions (Stevens Johnson syndrome and acute generalised exanthematous pustulosis)
1 Aug 2014 Oral ketoconazole: Safety updates on the risk of hepatotoxicity
2 Sep 2014 Cetrotide® (cetrorelix acetate): Change in storage condition from “at or below 25°C” to “2 - 8°C” to improve product stability
4 Sep 2014 Zaltrap® and Eylea® (afibercept): Potential risk for medication error between afibercept-containing products of Zaltrap® (formulated for intravenous use) and Eyelea® (formulated for intravitreal use)
5 Sep 2014 Tazpen® (piperacillin and tazobactam): Presence of particulate matter in vials of reconstituted Tazpen® from certain batches
2 Oct 2014 Xgeva® (denosumab 120mg): Updated recommendations for calcium monitoring related to the risk of severe symptomatic hypocalcaemia

29 Aug 2014 Synthes Transforaminal Posterior Atraumatic Lumbar Cage System (T-PAL): Update to the T-PAL technique guide to clarify instrument handling of the T-PAL Applicator
5 Sep 2014 Dura-Guard, Peri-Guard, and Vascu-Guard products: Reminder on the approved indications for Dura-Guard, Peri-Guard, and Vascu-Guard products, due to two recent reports involving use of the incorrect product during surgery
19 Sep 2014 COGNIS® CRT-Ds and TELIGEN® ICDs manufactured prior to December 2009: Update on subsets of COGNIS® CRT-Ds and TELIGEN® ICDs that experienced an increased rate of premature battery depletion due to compromised performance of a low voltage (LV) capacitor
22 Sep 2014 Zimmer Persona 48mm x 2.5mm Female Screw: Voluntary recall of all lots due to potential use of the screw in cortical bone, which may result in stripping of the 2.5mm Persona Hex Driver and subsequent issues during screw removal
23 Sep 2014 Cortex Screw Ø 3.5mm, length 28mm, stainless steel: Medical Device Recall for selected lots due to an identified manufacturing error
29 Sep 2014 ECHELON ENDOPATH™ Endoscopic Linear Cutter Reloads: Importance of following proper reload selection when using the device during surgical procedures, particularly laparoscopic sleeve gastrectomy, that involves the cutting and sealing of thicker tissue
1 Oct 2014 EDS 3™ CSF External Drainage System: Voluntary recall of all lots as the tubing within the system that drains cerebrospinal fluid (CSF) may leak or disconnect from the joints
27 Oct 2014 Alcon AcrySof® Cachet® Phakic Lens: Global discontinuation of market access due to increase in cases of endothelial cell loss (ECL) among clinical study patients with severe myopia

Season’s greetings from the Editor-in-chief

As the year draws to a close, we would like to thank all healthcare professionals for your active participation in the reporting of adverse events suspected to be associated with health products. Through your constant vigilance, we have managed to detect important safety signals and uncover several cases of adulterated complementary health products.

We recognise the importance of informing healthcare professionals on health product safety information in a timely manner so that you can make better informed decisions on the use of the affected health product. In addition to the HSA ADR News bulletin which most healthcare professionals would be familiar with, other safety-related information which are available on our website include safety alerts, product recalls, press releases, and abstracts of Dear Healthcare Professional Letters. We hope that the revamped HSA website will facilitate convenient access to such information.

The editorial team of the HSA ADR News bulletin wishes all our readers a brand New Year of opportunities, joy and good health!

Editor-in-chief
Chan Cheng Leng
Risk of hypoglycaemia associated with hydroxychloroquine or chloroquine

HSA would like to inform healthcare professionals about the risk of hypoglycaemia associated with the use of hydroxychloroquine or chloroquine. Hydroxychloroquine and chloroquine are antimalarial drugs used for the suppression and treatment of malaria. Hydroxychloroquine is also indicated for the treatment of rheumatoid arthritis, juvenile chronic arthritis, discoid and systemic lupus erythematosus and dermatological conditions caused or aggravated by sunlight. Chloroquine (Chloroquine®, Beacons Pharmaceuticals Pte Ltd) and hydroxychloroquine (Plaquenil®, sanofi-aventis Singapore Pte Ltd) have been registered in Singapore since 1988 and 2003, respectively. There are also two generic hydroxychloroquine-containing products registered locally, namely Dolquine® (Zyfas Medical Co) and Haloxin® (Pharmaforte Singapore Pte Ltd).

Background

Hydroxychloroquine is known to potentiate the hypoglycaemic effects of anti-diabetic agents. However, it has been reported in the literature that the risk of hypoglycaemia with hydroxychloroquine was also observed in patients who were not on concomitant hypoglycaemic agents. Two such case reports are highlighted below in patients who were prescribed hydroxychloroquine for the treatment of rheumatic diseases. In these case reports, hydroxychloroquine had been identified as the most likely cause of hypoglycaemia in these patients.

One overseas case report described a 62-year-old male patient with rheumatoid arthritis who was on sulphasalazine, methotrexate, prednisolone and leflunomide.1 Two months after hydroxychloroquine 200mg daily was added to his therapy, he developed hypoglycaemia (blood glucose level 10mg/dL or 0.56mmol/L) leading to unconsciousness. This patient was assessed to have developed hypoglycaemia secondary to hydroxychloroquine therapy after all predisposing conditions which could have led to the hypoglycaemic episode (e.g., insulinoma, ethanol intake, oral anti-diabetics, exogenous insulin usage) were ruled out. A second case report involved an 80-year-old female who reportedly had four events of hypoglycaemia leading to abrupt syncope and loss of consciousness.5 These events had all occurred within the four-month window period during which she was taking hydroxychloroquine 400mg daily. Her concomitant medications did not include any oral anti-diabetics or insulin. Upon discontinuation of hydroxychloroquine, no recurrence of the hypoglycaemia was reported in the 24-month follow-up period.

There was also a published overseas case report of hypoglycaemia associated with the use of chloroquine.1 In the report, the patient’s blood glucose level repeatedly fell below 36mg/dL (or 2mmol/L) despite repeated infusions with dextrose. While the dose and indication for chloroquine use was unknown, a post-mortem toxicological examination found levels of chloroquine to be within the range associated with death from chloroquine poisoning (57.2mg of chloroquine per 100g liver tissue). The authors postulated that the hypoglycaemia was associated with chloroquine poisoning.

The possible mechanisms by which hydroxychloroquine or chloroquine can lead to hypoglycaemia are supported by in vitro and animal studies. In vitro evidence has shown that chloroquine reduces intracellular insulin degradation, increases intracellular insulin accumulation, slows receptor recycling and stimulates insulin-mediated glucose transport. In animal studies, chronic chloroquine treatment was found to enhance insulin release in rats while treatment of diabetic rats with hydroxychloroquine led to higher insulin levels and lower glucose concentrations.1

International situation

In October 2013, following the European Medicines Agency’s review of information available in EudraVigilance and the literature, it was recommended that the product labelling for hydroxychloroquine and chloroquine should be strengthened on the risk of hypoglycaemia associated with their use.4 More recently, in July 2014, Health Canada has also concluded from its assessment that there is sufficient evidence to support a causal association between hydroxychloroquine use and the onset of hypoglycaemia, including serious cases involving a loss of consciousness and hospitalisation.1

Local situation and HSA’s advisory

To date, HSA has not received any adverse drug reaction reports of hypoglycaemia associated with hydroxychloroquine or chloroquine use. Healthcare professionals are advised to be vigilant to possible signs and symptoms of hypoglycaemia in patients prescribed hydroxychloroquine or chloroquine, regardless of concomitant use of hypoglycaemic agents. HSA is working with the companies to strengthen existing warnings in the local package inserts for hydroxychloroquine- or chloroquine-containing products regarding the additional information on the risk of hypoglycaemia.

References

1. Rheumatology 2008; 47: 378-9
2. BMJ Case Rep. 2011; PMC3207745

Please send your enquiries, comments and suggestions to:
Vigilance and Compliance Branch
Health Products Regulations Group
Health Sciences Authority
11 Biopolis Way, #11-01, Helios, Singapore 138667
Tel: (65) 6866 3538
Fax: (65) 6748 9069
Website: http://www.hsa.gov.sg
Email: HSA_productsafety@hsa.gov.sg

All website references were last accessed on 28 Nov 2014.

The contents are not to be reproduced in part or in whole, without prior written approval from the editor. Whilst every effort is made in compiling the content of this publication, the publishers, editors and authors accept no liability whatsoever for the consequences of any inaccurate or misleading data, opinions or statements. The mention of any product by the authors does not imply any official endorsement of the product by the Health Sciences Authority. Copyright © 2014 Health Sciences Authority of Singapore. All Rights Reserved.