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Adverse Drug Reaction News

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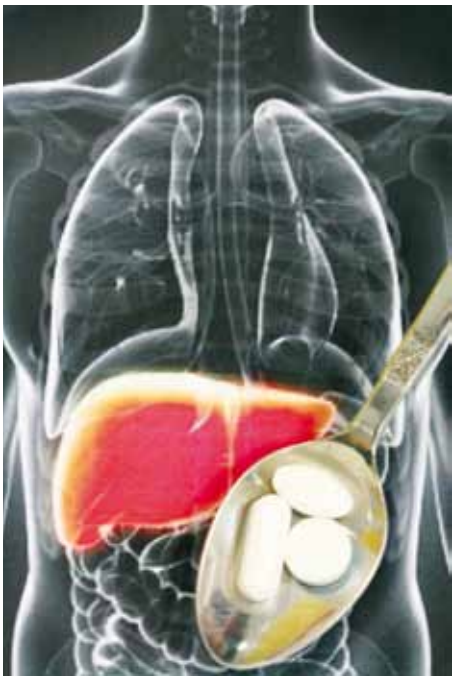
Safety advisory on oral ketoconazole
Additional measures to mitigate the risk of hepatotoxicity



HSA would like to update healthcare professionals on the outcomes of its benefit-risk assessment on oral ketoconazole. Warnings and recommendations for liver function monitoring will be strengthened in the local package inserts (PIs) to mitigate the risk of hepatoxicity with this drug. This decision was made in consultation with HSA's Medicines Advisory Committee (MAC) and clinical experts, following concerns raised internationally on liver toxicity associated with oral ketoconazole.

Ketoconazole is an azole antifungal indicated for the treatment of superficial infections of the skin, hair and mucosa, as well as systemic fungal infections, in patients whom the potential benefits for the use of the drug are considered to outweigh the potential risks, after taking into consideration the availability of other antifungal therapies. Janssen, a division of Johnson & Johnson Pte Ltd, has cancelled the Singapore product licence for Nizoral® (ketoconazole) 200mg tablets in October 2013, citing availability of alternative treatments. Currently, there are 10 generic oral ketoconazole-containing products registered in Singapore.

Background

The French National Agency for the Safety of Medicine and Health Products (ANSM) suspended the use of oral ketoconazole in 2011 and the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recommended its suspension throughout the European Union in July 2013.[1] These regulatory decisions were made following independent benefit-risk assessments by both agencies which concluded that the benefits of oral ketoconazole for treating fungal infections did not outweigh its risks due to the concerns on liver toxicity compared to other alternative treatments. In Australia, the product licence of the only oral ketoconazole-containing product, Nizoral®, was voluntarily withdrawn by the sponsor.[2]

Ketoconazole continues to be available in the US and Canada although the US Food and Drug Administration (FDA) and Health Canada (HC) had in 2013 restricted the indications of oral ketoconazole to serious systemic fungal infections when alternative antifungal therapies were not available or tolerated, and for treatment of severe, recalcitrant dermatophytoses unresponsive to other forms of therapies, respectively. In addition to updating safety information in the PIs for assessing and monitoring patients for liver toxicity, the US FDA added a new contraindication for patients with acute or chronic liver disease,[3] while HC advised mandatory liver function testing.[4]

HSA's benefit-risk assessment

HSA's review took into consideration expert opinions from infectious disease physicians, dermatologists, O&G specialists and family physicians, local ADR reports, scientific literature related to ketoconazole-associated hepatotoxicity, and actions taken by other regulatory agencies. It also took into account the availability of other alternative therapies.

Hepatotoxicity is a known adverse effect of ketoconazole although its incidence was reported as uncommon in the Singapore PI. It was noted that while safety data from a cohort study showed that the risk of acute liver injury is highest with ketoconazole,[5] there may be imbalances in the study design due to sample sizes and person-months duration of use. There was also uncertainty in quantifying precise estimates of risk, due to other methodological limitations such as lack of assessment of confounders and retrospective nature of the study.

HSA has received four local adverse reaction reports of hepatotoxicity (one case each of hepatitis and hepatitis cholestasis, and two cases of jaundice) over the past five years. The causality for all cases was assessed as possible, although the hepatitis case was confounded by concomitant administration of phentermine.

Based on the local physicians' input, there remains a place in therapy for oral ketoconazole for the treatment of fungal infections in Singapore. HSA, in consultation with its MAC, has concluded that the benefit-risk profile of oral ketoconazole for treatment of fungal infections remains favourable if additional measures were taken to mitigate the risk of hepatotoxicity. These include reinforcing that oral ketoconazole should only be used as last-line therapy for patients who have failed or who are intolerant to other therapies, and strengthening the warnings and recommendations for liver function monitoring in the local PIs.

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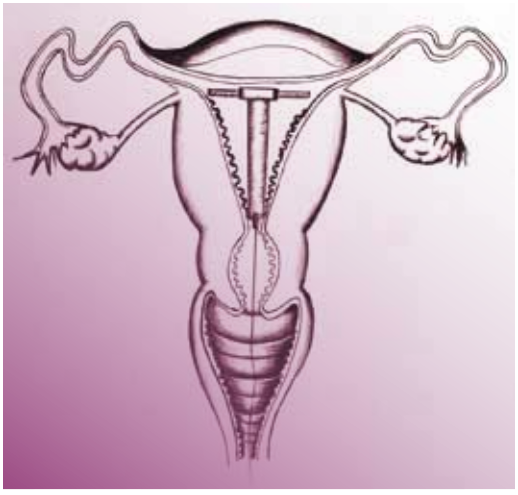
Update on risk of uterine perforation with intrauterine devices

HSA would like to inform healthcare professionals about the final findings from the European Active Surveillance Study for Intrauterine Devices (EURAS-IUD), which showed a higher risk of uterine perforation associated with both levonorgestrel-intrauterine system (LNG-IUS) and copper intrauterine devices (Cu IUDs) in breastfeeding women, as well as in women who are up to 36 weeks post-partum at time of insertion. The uterine perforation rate with the devices in the entire study population was classified as uncommon (1.3 per 1,000 insertions).



Schematic diagram of an intrauterine device inserted into the uterus

The LNG-IUS registered in Singapore since 1994 is Mirena® (Bayer (South East Asia) Pte Ltd), and the Cu IUDs, registered locally since 2005 and 2010, respectively, are Nova T® (Bayer (South East Asia) Pte Ltd) and Multilan AG Multiload cu250 and cu375 (MSD Pharma (Singapore) Pte Ltd). All the IUDs are indicated for contraception, with Mirena® having additional indications of idiopathic menorrhagia and protection from endometrial hyperplasia during oestrogen replacement therapy.

Background

Uterine perforation is a rare but serious complication of IUD insertion. The rate of uterine perforation per 1,000 insertions has been reported at 0.9 with LNG-IUS[1] and 0.6–1.6 with Cu IUDs.[2,3] Potential risks of uterine perforation such as insertion of IUDs in the first six months post-partum, lactation, and women with an atypical uterine anatomy (such as fixed retroverted uterus) have been reported.[2,4]

Breastfeeding has been reported in the literature as a potential risk factor for uterine perforation because of low serum oestrogen levels and therefore a more contracted uterus. A pooled analysis of uterine perforation after insertion of LNG-IUS from four national pharmacovigilance centres from 1990 to 2007 found that 42% of 462 women were breastfeeding at the time the perforations were discovered.[5]

Findings from the EURAS-IUD study

The EURAS-IUD is a prospective, non-interventional cohort study conducted from 2006 to 2013 in over 61,000 IUD users (70% LNG-IUS, 30% Cu IUDs) from six European countries. The study found that the incidence rate of uterine perforation was 1.3 per 1,000 insertions (95% CI 1.1, 1.6) in the whole study population. Breastfeeding at time of insertion led to a six-fold increase in total perforation risk, regardless of time interval since last delivery (risk ratio 6.1; 95% CI 3.9, 9.6). Insertion up to 36 weeks post-partum was also independently associated with an increased risk of perforation. The incidence of perforation with IUDs inserted at 36 weeks or less after delivery was 5.6 per 1,000 insertions (95% CI 3.9, 7.9) in breastfeeding women and 1.7 (95% CI 0.8, 3.1) in non-breastfeeding women, and dropped to 1.6 (95% CI 0.0, 9.1) and 0.7 (95% CI 0.5, 1.1), respectively when the insertions were performed at more than 36 weeks after delivery. These risks were independent of the type of IUD inserted.

Local situation

To date, two reports of uterine perforation associated with Mirena® were reported to HSA in 2011 and 2013. One case presented with heavy menstrual bleeding, while another case reported that Mirena® could not be located by thread pulling during its removal procedure. In both cases, the breastfeeding status of the patient was unknown. There were no local reports of uterine perforation associated with Cu IUDs. A Dear Healthcare Professional Letter was issued on 14 May 2014 by Bayer, who funded the EURAS-IUD, to update healthcare professionals on the study findings.[6]

HSA's advisory

Healthcare professionals are advised to take the above information into consideration when selecting IUDs for use in women who are less than 36 weeks post-partum or breastfeeding at time of insertion.

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Safety advisory on oral ketoconazole

HSA's advisory

Healthcare professionals are advised to take note of the following to minimise the risk of ketoconazole-associated hepatotoxicity:

- Ketoconazole should only be used in patients who have failed or who are intolerant to other therapies for superficial fungal infections of the skin, hair and mucosa, and systemic fungal infection.
- Serious hepatotoxicity was reported by patients receiving high doses for short treatment durations and those receiving low doses for long durations.
- Patients should be advised against alcohol consumption while on ketoconazole treatment. If possible, concomitant use with other potentially hepatotoxic drugs should be avoided.
- During the course of treatment, serum alanine aminotransferase (ALT) should be monitored weekly. If ALT values increase above the upper limit or 30% above baseline, or if the patient develops symptoms, ketoconazole treatment should be interrupted and a full set of liver tests should be obtained.

HSA will be working with the companies to update the local PIs of oral ketoconazole-containing products to reflect the above recommendations. A Dear Healthcare Professional Letter was issued on 1 August 2014 to advise healthcare professionals on these new recommendations.[6]

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Overseas recommendations on the use of codeine-containing products for pain relief in paediatric patients

HSA would like to provide an interim update on the new contraindication and precautionary recommendations issued by the US Food and Drug Administration (FDA), European Medicines Agency (EMA) and Health Canada on the use of codeine-containing products in paediatric patients for pain relief. EMA is also separately reviewing the use of codeine-containing preparations used for cough or cold in children,[1] and its recommendations are expected at the end of 2014. HSA is currently reviewing the use of codeine-containing preparations in children in totality, covering both pain relief as well as cough suppression for the relief of unproductive cough and will advise our healthcare professionals on the recommendations relevant to our local context in due course.

Background

In August 2012, the US FDA reviewed the use of codeine following reports of three deaths and a case of severe respiratory depression in young children (aged 2 to 5 years old) who received codeine following tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome.[2] These children had evidence of being "ultra-rapid metabolisers" of substrates of CYP2D6, which include codeine, and they may have been particularly sensitive to the respiratory depressant effects resulting from the increased conversion of codeine to morphine. Data from the US FDA's Adverse Event Reporting System database, from 1999-2012, identified a further 10 cases of paediatric death and three cases of drug overdose associated with codeine use. Of these, three were ultra-rapid metabolisers, three were extensive metabolisers and one was a likely ultra-rapid metaboliser. Eight of the cases involved adenotonsillectomy.[3] In August 2007, the US FDA reported the death of a healthy breast-fed 13-day-old baby, whose mother was taking a low dose of codeine for episiotomy pain. The mother was found to be an ultra-rapid metaboliser of codeine and the baby was shown to have high blood levels of morphine which was consumed through breast milk.[4]

Recommendations by US FDA and other regulatory authorities

Following its review of the safety profile of codeine, the US FDA enhanced the label warnings regarding the use of codeine in paediatric patients. Subsequently, other regulatory agencies such as the EMA and Health Canada announced similar recommendations on restricting the use of codeine for pain relief in children. Table 1 summarises the new label recommendations by the US FDA, EMA and Health Canada.

Table 1. New label recommendations by overseas agencies

	US FDA[3]	EMA[5]	Health Canada[6]
Post-operative pain after tonsillectomy and/or adenoidectomy	Contraindicated in all children (≤ 17 years old)	Contraindicated in patients < 18 years old	Not recommended in patients < 12 years old regardless of clinical setting
General management of other types of pain	Use only if benefits outweigh risks	≤ 12 years old: Not recommended >12 years old: Restrict to treatment of acute moderate pain not relieved by other analgesics (e.g., paracetamol, ibuprofen)	
Other recommendations	Closely monitor children for signs of morphine overdose (e.g., unusual sleepiness, confusion, difficult or noisy breathing), and seek medical attention immediately if these signs are observed	Children with breathing problems should not use codeine Codeine should not be used by nursing mothers Codeine should not be used by people of any age who are known to be ultra-rapid metabolisers	Caution is advised when codeine is administered to nursing mothers

Local situation

To date, HSA has not received any local adverse event report of respiratory depression associated with the use of codeine in children. HSA is embarking on a review of codeine-containing preparations in Singapore for pain relief as well as the relief of cough symptoms in children, taking into account the recommendations made by international regulatory agencies. In the meantime, healthcare professionals are advised to exercise caution when codeine is administered to paediatric patients. HSA will provide an update on the outcome of our review when it is completed.

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MEDICAL DEVICE INFORMATION UPDATE (1)

Overview of the US FDA medical device regulations

This article provides a brief overview of the US Food and Drug Administration's (FDA) clearance and approval process for medical devices. This is the first of a series of articles which HSA will be communicating on medical devices and their regulation to enhance the understanding of our healthcare professionals on the various issues associated with these products.

Medical Device Amendments of 1976

The regulatory framework for medical devices in the US was first established via the Food, Drugs and Cosmetics Act of 1938, where the regulation of medical devices was mostly limited to protecting consumers against false labelling, spurious claims and fraud. By the 1970s, the original regulatory system was no longer adequate or flexible enough to deal with the increasing sophistication and variety of new devices, leading to the passing of the Medical Device Amendments of 1976 (MDA). It should be noted that the MDA was based on the premise that devices with a long market history were generally safe, and was framed in an environment where medical devices were less complex, and before technological advancements such as the internet, automatic external defibrillator and robotic surgery.

The MDA legally defined medical devices and provided for all medical devices to be classified into three risk classes. Medical devices were also divided into pre-amendment and post-amendment devices, so that pre-amendment devices (i.e. devices legally distributed before 28 May 1976) were not subject to the new legal requirements as they were considered to be "grandfathered" devices. Post-amendment devices were required to undergo premarket evaluation and approval, unless their manufacturers could demonstrate that the devices were "me-too" (substantially equivalent) to either pre-amendment devices or other post-amendment devices that were legally US marketed and not subject to premarket approval. Devices that fulfilled this condition were cleared to be marketed without going through an in-depth premarket review, subject to any future or existing requirements for that type of device. The majority of post-amendment devices have gained market access through this "510(k)" notification route, named after the enabling Section 510(k) of the Food, Drugs and Cosmetics Act.

Classification of medical devices in the US

The US FDA requires all medical device manufacturers to register their establishments (i.e. facilities involved in the production and distribution of medical devices intended for use in the US) and list their devices with the Agency. Medical devices are classified into three risk classes based on the risks posed to consumers and the regulatory controls necessary to ensure safety (Table 1).

There are also two additional classifications – "De Novo" and Humanitarian Device Exemption (HDE). De Novo devices are devices which have never been marketed in the US (i.e. new device) but whose safety profile and technology are reasonably well understood. HDE devices are used for orphan diseases, where the prevalence of the condition for which the device is indicated is less than 4,000 patients per year in the US.

Medical device marketing application

Before a medical device may be legally marketed in the US, the manufacturer is required to submit an application to the US FDA via one of three pathways:

- **510(k) exempted devices** – applicable to mainly Class I and some Class II devices
- **510(k) clearance** – requires proof that the device is substantially equivalent to a legally marketed device that is not subject to premarket approval
- **Premarket approval (PMA)** – requires documented safety and effectiveness data for the intended use of the device

1) 510(k) exempted devices

The FDA Modernisation Act of 1997 redefines the criteria under which Class I and II devices can be exempted from premarket notification requirements. Devices which are exempted from 510(k) requirements include pre-amendment devices, Class I and II devices that are exempted by statutes subject to limitations,[1] devices not sold in the US, private label devices which have already received clearance for the original devices, and custom made devices.

2) 510(k) clearance

More than 90% of medical devices requiring premarket clearance gain access to the US market through the 510(k) clearance pathway. The applicant must demonstrate that the device to be marketed is substantially equivalent to an already marketed device which does not require PMA (referred to as a "predicate"). A predicate device can be a pre-amendment device, a device which FDA determines to be substantially equivalent, a reclassified Class I or II device, or a device classified by a de novo petition.

To fulfil the condition of substantial equivalence, the device and its predicate must have the same intended use, the same but not necessarily identical technological characteristics, and must not raise additional questions of safety and effectiveness. It is important to understand that the 510(k) process was not employed to determine the safety and effectiveness of a new device, but to determine its similarity to existing devices, whose safety and effectiveness may or may not have been evaluated. The device is assumed to be safe or effective based on its similarity to the predicate device, rather than

Table 1. Classification of medical devices in the US

Category	Level of risk	Examples	Regulatory controls	Required submission
Class I	Lowest risk	Bandages, stethoscopes, X-ray films	General control[a]	Mostly exempt from either the 510(k) process or premarket review If not exempted, 510(k) clearance required
Class II	Moderate risk	Non-life sustaining devices which must meet specified performance standards, e.g., blood pressure monitors, infusion pumps, endoscopes, ultrasonic devices, radiation treatment systems, CT X-Ray systems, ventilators	General control and Special control[b]	Most can be marketed after submission of premarket notification through the 510(k) process Substantially equivalent to predicate
Class III	Highest risk	Devices used in supporting or sustaining life, e.g., cardiac stents, heart valves, left ventricular assist devices, pacemakers	General control and Premarket approval	Safety and effectiveness clinical data

[a] *General control includes prohibition against adulteration, misbranding, pre-market notification requirements, good manufacturing practices, registering of manufacturing facilities, listing of devices, record keeping*

[b] *Special control includes guidance, performance standards, post-market surveillance, patient registries*

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■ **Overview of the US FDA medical device regulations** ■

having to demonstrate safety and effectiveness independently through clinical studies.

3) Premarket approval (PMA)

Devices which cannot be cleared for the market through the 510(k) clearance pathway are required to have PMA and are automatically classified as Class III devices. The requirement for PMA is more stringent than 510(k) clearance and must be substantiated through additional clinical and non-clinical studies, manufacturing methods and design review. The applicant must also demonstrate the safety and effectiveness of the device, and post-market studies requirements are usually integral to the approval conditions.

Review of the 510(k) process

Arising from numerous safety and performance concerns for medical devices over the years, various criticisms from policymakers and patients have been raised against the 510(k) process. As a result, the US FDA commissioned the Institute of Medicine (IOM) of the National Academy of Sciences to review its 510(k) process in September 2009. The IOM's report, released in July 2011, concluded that "the 510(K) clearance is not a determination that the cleared device is safe or effective".[2] The committee also concluded that "the FDA's finite resources would be better invested in developing an integrated premarket and post-market regulatory framework that provides a reasonable assurance of safety and effectiveness throughout the device life cycle". In response to the IOM's recommendations, the US FDA has opted to enhance the current process instead of eliminating the 510(k) pathway. As outlined in its 510(k) preliminary report, this reform process includes creating new or updating existing guidances for clarity, taking steps to foster the submission of high-quality 510(k) device information, enhancing its databases to provide more complete, up-to-date device information, and developing programme metrics and better systems to support continuous quality assurance of the 510(k) process.[3]

Conclusion

The regulation of medical devices is complex, partly due to the wide variety of products that are categorised as medical devices, ranging from a simple elastic bandage to a life-sustaining heart valve. No medical device is completely safe and the regulatory process to ensure and protect public safety varies with different regulatory agencies in accordance to their regulatory framework.

In its evaluation of medical devices, HSA gives recognition to devices that are registered by the five reference agencies which founded the Global Harmonisation Task Force, namely US FDA, EU, Australia's Therapeutic Goods Authority, Health Canada and Japan's Ministry of Health, Labour and Welfare. However, this recognition does not extend to the acceptance of the device for automatic registration in Singapore. Such devices are instead accepted for abridged evaluation. HSA will continue to review its medical device regulatory framework to ensure that safe, effective and quality medical devices are introduced and accessible in Singapore.

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Further reading

1 US FDA website
  a PMA approval
  http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm048168.htm
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  http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM284443.pdf
2 Congressional Research Service – FDA Regulation of Medical Devices
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Lithium and the risk of hypercalcaemia and hyperparathyroidism

HSA would like to share with healthcare professionals a recent advisory issued by Health Canada regarding the risk of hypercalcaemia associated with lithium therapy, which may or may not be accompanied with hyperparathyroidism. Lithium has been registered locally since 1988 as Camcolit-400® (Apex Pharma Marketing Pte Ltd) for the treatment and prophylaxis of mania, manic-depressive illness and recurrent depression.

Background

Rates of lithium-induced hypercalcaemia have been estimated to be between 5% to 40%.[1] While the effects of high blood calcium and/or parathyroid hormone (PTH) may be unnoticeable or mild in many cases, they can be life threatening in severe cases, leading to medical emergencies such as coma and cardiac arrest.[2, 3]

In a published systematic review and meta-analysis of studies investigating the association between lithium and all reported major adverse effects, the authors found a 10% increase in blood calcium (+0.09mmol/L; 95% CI 0.02, 0.17; p=0.009) and PTH (+7.32pg/mL; 95% CI 3.42, 11.23; p<0.0001) values when compared with normal values, in patients given lithium compared with controls.[4] The increase was postulated to be attributed to lithium's inactivation of the calcium-sensing receptor and interference with intracellular second messenger signalling. This effect leads to an increased release of PTH, which raises blood calcium concentration.

Review by Health Canada

Based on its review, Health Canada has reaffirmed that the benefits of lithium therapy in the treatment of bipolar disorder continue to outweigh the known risks of this drug. The agency had recommended reviewing patient calcium blood levels at the following times: before the start of lithium treatment, six months after initiation of lithium and subsequently on an annual basis for patients on long-term treatment. Healthcare professionals were also advised to consider measuring the PTH blood levels, if necessary, to identify or rule out hyperparathyroidism.

Local situation and HSA's advisory

To date, HSA has received one adverse drug reaction report of hyperparathyroidism with lithium use. There were no reports relating to hypercalcaemia suspected to be associated with lithium use. Hypercalcaemia and hyperparathyroidism are both known risks associated with lithium therapy, which have already been highlighted in the local package insert of Camcolit-400®. Healthcare professionals may wish to consider the above information in the management of their patients and be vigilant to possible signs and symptoms of hypercalcaemia and hyperparathyroidism in patients prescribed lithium.

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Update on risk of thromboembolism associated with combined hormonal contraceptives

HSA would like to update healthcare professionals on the outcome of its review on the risk of thromboembolism associated with combined hormonal contraceptives (CHCs). Although venous thromboembolism (VTE), which includes deep vein thrombosis and pulmonary embolism, is a known potential risk with the use of CHCs, current evidence showed that the small absolute risk of VTE associated with CHCs may differ depending on the type of progesterone present in the preparation. CHCs are also associated with an increased risk of arterial thromboembolism (ATE) but there is insufficient evidence to demonstrate if the ATE risk varies between different CHCs.

Relative risks of CHCs

HSA's review focused on the 'third- and fourth-generation' CHCs, which have been registered in Singapore since 1990. These CHCs contain newer progesterones at lower doses as compared to the 'first- and second-generation' CHCs (e.g., those containing norethisterone and levonorgestrel, respectively), thus resulting in fewer adverse effects such as weight gain, fluid retention, and headaches. The progesterone contained in the 'third- and fourth-generation' CHCs includes desogestrel, dienogest, drospirenone, etonogestrel, gestodene, nomegestrol, norelgestromin or norgestimate, which are combined with varying doses of ethinylestradiol or estradiol. There are 11 brands of these CHCs registered locally in various formulations such as oral tablet, transdermal patch or vaginal ring (Table 1).

Table 1. 'Third- and fourth-generation' CHCs registered locally

Active ingredients	Brand name
Desogestrel/Ethinylestradiol	Gracial®, Marvelon®, Mercilon®
Dienogest/Estradiol	Qlaria®
Drospirenone/Ethinylestradiol	Yasmin®, Yaz®
Etonogestrel/Ethinylestradiol	Nuvaring® vaginal ring
Gestodene/Ethinylestradiol	Gynera®, Meliane®
Nomegestrol/Estradiol	Zoely®
Norelgestromin/Ethinylestradiol	Evra® transdermal patch
Norgestimate/Ethinylestradiol	Not registered locally

Based on scientific evidence to date, CHCs containing levonorgestrel, norethisterone and norgestimate have the lowest VTE risk. Estimates of the relative risk of VTE with different generations of CHCs compared with that for levonorgestrel-containing CHC (a 'second-generation' CHC) are provided in Table 2.[1]

Table 2. Risk of VTE with CHCs

Progesterone in CHC	Relative risk versus levonorgestrel-containing CHC	Estimated incidence (per 10,000 women-years)
Non-pregnant non-user	–	2
Levonorgestrel	Reference	5–7
Norgestimate, Norethisterone*	1.0	5–7
Desogestrel, Drospirenone, Gestodene	1.5–2.0	9–12
Etonogestrel, Norelgestromin	1.0–2.0	6–12
Dienogest, Nomegestrel	Not yet established. Further studies are ongoing or planned for data collection	Not yet established. Further studies are ongoing or planned for data collection

** There are no CHCs containing norgestimate or norethisterone registered in Singapore.*

The risk of ATE (myocardial infarction, cerebrovascular accident) is also known to be increased with the use of CHCs. In a large historical cohort study by Lidegaard *et al*, the relative risks for ischaemic stroke and myocardial infarction in users of CHCs versus non-users were 1.5–2.2 and 1.7–2.3, respectively.[2] However, there is insufficient evidence to demonstrate any difference in ATE risk between CHCs.

International regulatory actions

The European Medicines Agency's Pharmacovigilance Risk Assessment Committee completed its safety assessment in January 2014, which concluded that the benefit-risk balance of the reviewed products in the indication of contraception remains favourable.[1] The Committee recommended placing emphasis on the importance of an individual woman's risk factors and the need to assess them regularly, as well as raising awareness of the signs and symptoms of VTE and ATE which should be described to women when a CHC is prescribed.

HSA's advisory and actions

Healthcare professionals should take into consideration the latest evidence on the risk of thromboembolism associated with CHCs when discussing the most suitable type of contraceptive for their patient. Careful consideration should be given to the woman's risk factors for thromboembolism and these risk factors should be reassessed regularly. The risk of thromboembolism with a CHC is higher during the first year of use, and when re-initiating its use after a break of four or more weeks.

HSA is working with the companies to update the local package inserts of 'third- and fourth-generation' CHCs to reflect the current available information, including strengthening the contraindications for use, highlighting the difference in VTE risk of each product versus a levonorgestrel-containing CHC, and updating the baseline VTE rates. A Dear Healthcare Professional Letter was issued on 26 May 2014 to update healthcare professionals on HSA's review outcome.[3]

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2 *N Engl J Med 2012; 366: 2257-66*
3 *http://www.hsa.gov.sg/DHCPL*

List of Dear Healthcare Professional Letters (DHCPL) issued by HSA, pharmaceutical and medical device companies since the last HSA ADR bulletin

For details, please log on to MOHAlert via your professional board's website.

Therapeutic products

2 Apr 2014 **Topamax® (topiramate):**
Updated warnings and precautions on visual field defects

7 Apr 2014 **Dilatrend® (carvedilol):**
Risk of severe skin reactions

23 Apr 2014 **Zelboraf® (vemurafenib):**
Risk of drug-induced liver injury (DILI)

5 May 2014 **Vectibix™ (panitumumab):**
Risk of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)

14 May 2014 **Intrauterine devices:**
Updates on risk of uterine perforation with levonorgestrel-intrauterine system (LNG-IUS) and copper intrauterine devices (Cu IUDs)

19 May 2014 **Velcade® (bortezomib):**
Potential risk of cracked/broken vials

26 May 2014 **Tri-luma® cream (fluocinolone/hydroquinone/tretinoin):**
Change in storage condition

26 May 2014 **Trivastal Retard® (piribedil):**
Restriction of indication to treatment of Parkinson's Disease only

26 May 2014 **Combined oral contraceptives:**
Update on risk of thromboembolism

29 May 2014 **Engerix™-B and Infanrix™-IPV+Hib vaccines:**
Local isolated reports of stopper coring

2 Jun 2014 **Erbitux® (cetuximab):**
Importance of establishing wild-type RAS status before initiating treatment

9 Jun 2014 **Effient® (prasugrel):**
Increased risk of serious bleeding in patients with unstable angina/NSTEMI when administered prior to diagnostic coronary angiography

18 Jun 2014 **Kaletra® (lopinavir/ritonavir):**
Incorrect package insert attached with Batch 345028D

20 Jun 2014 **Protos® (strontium ranelate):**
Restricted indication and monitoring recommendations to mitigate the risk of cardiovascular disorders

1 Jul 2014 **Ventolin® (salbutamol):**
Limitations on use for inhibition of premature labour

3 Jul 2014 **Durogesic® (fentanyl):**
Reminder on the potential for life-threatening harm from accidental exposure to transdermal fentanyl

3 Jul 2014 **Arzerra® (ofatumumab):**
Safety update on fatal infusion reaction

11 Jul 2014 **Primperan® (metoclopramide):**
Updated indications and posology to minimise risk of adverse effects (particularly neurological effects)

Medical devices

27 Mar 2014 **DePuy S-ROM Noiles Rotating Hinge Femur with Pin:**
Package redesign due to potential for holes to develop in the inner and outer sterile pouches of the affected device

27 Mar 2014 **Thoratec® HeartMate II EPC System Controller and Pocket System Controller:**
Updates to Instructions for Use and Patient Handbook due to reports of serious patient injuries and deaths associated with the process of changing from a primary Pocket System Controller to a backup Pocket System Controller

8 Apr 2014 **SynchroMed® II Implantable Drug Infusion Pump Models 8637-20 & 8637-40:**
Important information regarding overinfusion which may result in life-threatening events due to drug overdose or may result in withdrawal syndromes

17 Apr 2014 **Osseofix Sterile Package Implants, Size 4.5mm, 5.5mm and 7.0mm:**
Urgent medical device recall for affected lots of packaged sterile single-use units that may contain used Osseofix Inserter Cannulas

5 May 2014 **Accu-Chek Compact Plus and Accu-Chek Mobile Blood Glucose Monitoring Systems:**
Labelling modifications due to the possibility of erroneously low blood glucose readings in patients undergoing ceftriaxone therapy

23 May 2014 **Medtronic Mosaic™ Aortic Bioprosthesis, Model Number 305:**
Important information on cases of higher-than-expected transvalvular gradients due to the practice of substantial oversizing, and corrective actions such as modifying of sizing charts to optimise sizing

6 Jun 2014 **Heartware® Ventricular Assist System:**
Corrective action taken due to an increase in power management complaints related to both premature battery failure and routine battery handling

23 Jun 2014 **Synthes Cortex Screw Ø 1.3/1.5 mm, self-tapping, length 8 mm sterile and non-sterile:**
Voluntary recall of selected lots due to a customer complaint regarding a wrong article contained within the packaging

26 Jun 2014 **Synthes Orbital Rim Plate 1.3, curved, 9 holes, Pure Titanium:**
Labelling correction of selected models due to their mislabelling as Orbital Floor Plates

27 Jun 2014 **Zimmer NexGen Complete Knee Solution MIS Total Knee Procedure Stemmed Tibial Component:**
Voluntary recall of specific identified lots due to the potential that the threads may be out of specification in these lots

23 Jul 2014 **Teosyal products:**
Update to Instructions For Use to communicate the risk of anaphylactic shock occurring in patients with potential contraindications

What to report? You don't need to be certain, just suspicious!

HSA encourages the reporting of all suspected adverse events to drugs and other medicinal substances (including herbal, traditional or alternative remedies). In particular, please report the following:

1 All serious adverse events which:
   a) are life threatening or fatal,
   b) require in-patient hospitalisation or prolong existing hospitalisation
   c) cause persistent or significant disability or incapacity
   d) lead to congenital anomalies
   e) are medically significant

2 All adverse events to recently marketed drugs that have been introduced into Singapore in the recent 5 years, regardless of their nature and severity

Please do not be deterred from reporting because some details are not known. Online reporting is available at *http://www.hsa.gov.sg/ae_online*. Forms can also be downloaded from the same website and submitted via the following methods:

- By mail to *Vigilance and Compliance Branch* (refer to full address on page 8)
- By fax to *(65) 6478 9069*
- By email to *HSA_productsafety@hsa.gov.sg*

New recommendations for simvastatin use in Asians based on findings from the HPS2-THRIVE study

HSA is recommending for the local package inserts of simvastatin-containing products to be updated to provide new recommendations for the use of simvastatin in Asians. These recommendations are based mainly on findings from the Heart Protection Study 2 – Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE),[1] which showed a higher rate of myopathy in the Chinese population.

Simvastatin is a HMG-CoA reductase inhibitor indicated as an adjunct to diet for dyslipidemia. In patients at high risk of coronary heart disease (CHD) or with existing CHD, it is indicated to reduce the risk of CHD death, non-fatal myocardial infarction and stroke, as well as to reduce the need for coronary and non-coronary revascularisation procedures.

Background

The HPS2-THRIVE study recruited over 25,000 patients with pre-existing cardiovascular disease from the UK, Scandinavia and China. It was designed to assess cardiovascular outcomes following addition of extended-release niacin/laropiprant 2g/40mg or placebo to simvastatin (with or without ezetimibe). No other statins were investigated in this study. Failure to achieve the study's primary endpoint of reducing cardiovascular events, coupled with a statistically significant increased risk of non-fatal serious adverse events, led to the worldwide withdrawal of niacin/laropiprant in January 2013.

A subsequent review of the study data revealed important observations about the use of simvastatin in Chinese patients, who formed 40% of the study population. This led to new precautions advising caution when prescribing simvastatin to Asian patients and that the lowest dose necessary should be employed. Although Chinese patients were the only Asians assessed in HPS2-THRIVE and data in other Asian populations is limited, MSD Pharma (Singapore) Pte Ltd, the local product licence holder for Zocor® (the innovator brand of simvastatin), had proposed for these new precautions for simvastatin use to be extended to all Asians, including Japanese, Malays and Asian-Indians, due to the potential seriousness of myopathy.[2]

Asian data from HPS2-THRIVE[2,3]

Overall, the risk of myopathy observed in HPS2-THRIVE was four times greater with niacin/laropiprant and simvastatin compared to simvastatin alone (0.58% vs 0.13%, p<0.0001). This difference was primarily driven by a higher occurrence of myopathy in Chinese patients, where the incidence with dual therapy was 1.24% compared to 0.24% in the simvastatin control group (p<0.0001). In Europe, the incidence was 0.05% and 0.03%, respectively. However, the results did not show statistical significance (p=0.37).

To date, the specific cause of the increased susceptibility of Chinese patients to myopathy has not been identified Other studies have shown a trend of marginally higher exposure of simvastatin and its active metabolite, simvastatin acid, in Asians compared to non-Asian subjects taking simvastatin.[2] However, the higher myopathy rates in Chinese patients taking both simvastatin and niacin/laropiprant did not correspond with higher exposure of simvastatin compared to non-Asians taking this drug combination. This suggests there may be other factors apart from pharmacokinetics that could cause an increase in myopathy among Chinese patients. Previous studies have shown that polymorphisms in the SLCO1B1 gene are associated with an increase in myopathy due to their effect on the metabolism of simvastatin. However, the prevalence of variants appears to be similar in Asian and European population. Thus, this genetic factor currently does not explain the differential risk observed.

HSA's advisory and actions

The benefit-risk profile of simvastatin remains positive when used for its licensed indications. Healthcare professionals are advised to prescribe simvastatin with caution to Asian patients and to use the lowest dose necessary. In addition, co-administration of simvastatin with lipid modifying doses (>1g/day) of niacin is not recommended in Asian patients. As the data supporting these new recommendations arose from the HPS2-THRIVE study that did not investigate other statins, it is not known at this point if these findings can be extrapolated to other statins. In the meantime, HSA is working with the companies to update the new recommendations in the local package inserts of all simvastatin-containing products.

References

1 *Eur Heart J 2013; 34: 1279-91*
2 *Clinical overview provided by MSD Pharma (Singapore) Pte Ltd to HSA*
3 *Singapore package insert for Zocor®. Approved 26 Mar 2014*

Please send your enquiries, comments and suggestions to:

Vigilance and Compliance 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 25 July 2014.