ISSN: 0219 - 2152 Dec 2016 Vol.18 No.3

ADVERSE DRUG REACTION NEWS

HSA Health Sciences Authority

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REVISED INDICATION ON THE USE OF RISPERIDONE FOR TREATMENT OF DEMENTIA

Key Points

- Benefit-risk assessments of risperidone-containing products by international regulatory agencies and HSA confirmed a relationship between the use of risperidone in mixed or vascular dementia and an increased risk of cerebrovascular adverse events
- The licensed indication of risperidone will be revised to the short term treatment of persistent aggression in patients with Alzheimer's Dementia only
- Healthcare professionals are advised to take them into consideration when prescribing risperidone-containing products

HSA would like to update healthcare professionals on the outcomes of its benefit-risk assessment on the revised indication of risperidone for the treatment of dementia.

Risperidone is currently approved for the treatment of behavioural disturbances in patients with dementia. In view of increased risk of cerebrovascular adverse events (CVAE) associated with its use in mixed or vascular dementia (MD/VD), the licensed indication of risperidone will be revised to the short-term treatment of persistent aggression in patients with Alzheimer's Dementia (AD) only. It will no longer be recommended for use in other types of dementia, such as MD/VD. In addition, warnings will be strengthened in the local package inserts to mitigate the risk of CVAE. This regulatory action was made in consultation with HSA's Medicines Advisory Committee (MAC) and clinical experts, following concerns raised internationally on increased risk of CVAE associated with the use of risperidone in MD/VD.

Background

Several other international drug regulatory agencies have similarly restricted the indication of risperidone, following the initiation on the change in the licensed indications submitted by the manufacturer (Janssen Cilag Spa) of the innovator product (Risperdal®). These include Health Canada[1] and the Australian Therapeutics Goods Administration.[2] The European Medicines Agency has further limited the duration of use of risperidone for short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe AD unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others.[3]

HSA's benefit-risk assessment

HSA's benefit-risk assessment on the use of risperidone for the treatment of dementia, took into consideration current available scientific evidence, inputs from local clinicians, safety data submitted by product licence holder (Johnson & Johnson Pte Ltd), local adverse drug reaction (ADR) reports and the actions taken by other drug regulatory agencies.

Available data showed that risperidone, at recommended therapeutic doses, demonstrated efficacy in treatment of aggression in elderly patients with moderate to severe dementia

(AD, MD or VD) by achieving statistically significantly greater response rates measured by Behaviour Pathology in Alzheimer's Disease (BEHAVE-AD) and Cohen-Mansfield Agitation Inventory (CMAI) scores versus placebo.

CVAE such as stroke and transient ischemic attack, including fatalities, had been reported in trials of risperidone in elderly patients with dementia-related psychosis. However, the assessment of the post-market data showed that there was a higher incidence of CVAE in MD/VD versus AD patients taking risperidone. Pooled results from all placebo-controlled studies showed that CVAE risk was increased 2.1 times in MD/VD patients compared to AD patients. Pooled data from all placebo-controlled studies also showed that the number of serious CVAE could be increased by 2.7 times in MD/VD compared to AD patients. While the cause of the CVAE in these patients is unknown, the increase in CVAE risk in dementia patients had been postulated to be due to orthostatic hypotension, thromboembolic events and dehydration etc.[4] In addition, concomitant diseases such as poorly controlled diabetes and hypertension as well as underlying cerebral pathology such as in VD also predispose patients to CVAE.

HSA has received one serious ADR report of stroke associated with risperidone. A 92-year old, diagnosed with behavioural and psychotic symptoms of dementia, was prescribed risperidone for behavioural control for 6 months. The patient also had other risk factors such as hyperlipidaemia. In addition, the patient had osteoarthritis of the knees, vestibulobasilar insufficiency and benign prostatic hyperplasia. However, risperidone was the only suspected drug and the causality was assessed by the reporting doctor as possible.

HSA, in consultation with its MAC, concluded that the benefit-risk profile for use of risperidone in treatment of aggression in dementia remains favourable when it is restricted for the short-term treatment of AD. Considerations include the assessment that the CVAE risk for AD had not been shown to be elevated against what is currently known for the drug. In addition, when using risperidone in AD, CVAE risk may be mitigated by the physician's assessment of cerebrovascular risk factors, tailing off treatment when behavioural and psychotic symptoms of dementia is controlled and regular follow-up to assess patient and need for continued treatment. However, risperidone is no longer recommended for use in other types of dementia, such as MD/VD, due to increased CVAE risk.

HSA's advisory

Healthcare professionals are advised to take note of the following to minimise the risk of CVAE when considering the use of risperidone for the treatment of dementia:

- Risperidone is indicated for the short-term treatment of persistent aggression in patients with moderate to severe dementia of the Alzheimer's type unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others.
- The risk of CVAEs was higher in patients on risperidone with mixed or vascular type of dementia when compared to Alzheimer's Dementia.
- Physicians are advised to assess the risks and benefits of the use of risperidone in elderly patients with dementia, taking into account risk predictors for stroke in the individual patient.
- Patients should be re-assessed regularly to determine the need for continued treatment.

HSA will be working with the companies to update the local package inserts of risperidone products to reflect the restriction in indication and recommendations. A Dear Healthcare Professional Letter was issued on 16 June 2016 to advise healthcare professionals on these recommendations.[5]

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HLA-B*1502 GENOTYPING AND CARBAMAZEPINE-INDUCED SEVERE CUTANEOUS ADVERSE REACTIONS

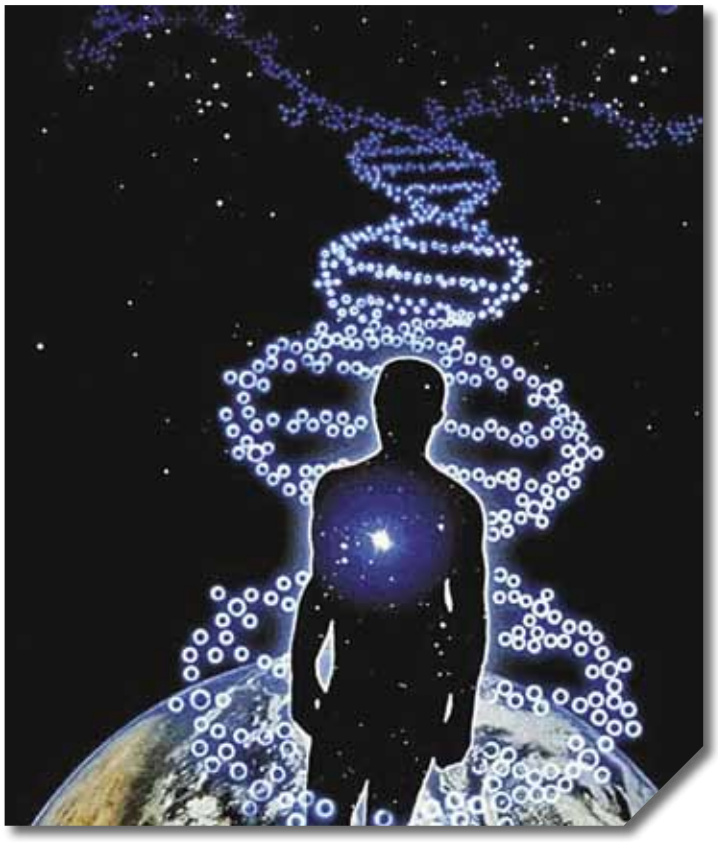
Key Points

- In a joint advisory issued with HSA in April 2013, MOH stated that genotyping for the HLA-B*1502 allele prior to the initiation of carbamazepine (CBZ) therapy in new patients of Asian ancestry is now considered the standard of care
- HLA-B*1502 genotype testing identifies patients at high risk of developing Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis (SJS/TEN) who are initiating CBZ therapy. The incidence of CBZ-induced SJS/TEN locally has declined significantly following the genotyping recommendation
- Although reported to be rare, patients tested negative for HLA-B*1502 can still develop SJS/TEN. HLA-B*1502 has not been shown to be a risk predictor for Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)
- Healthcare professionals are reminded to be vigilant for CBZ-induced severe cutaneous adverse reactions including DRESS, especially during the first 12 weeks following the initiation of CBZ therapy

Introduction

Carbamazepine (CBZ) is an anticonvulsant indicated for the treatment of epilepsy and other conditions such as bipolar disorders, alcohol-withdrawal syndrome, trigeminal neuralgia, diabetic neuropathy and diabetes insipidus centralis. It has been registered in Singapore since 1988 and there are currently nine registered CBZ-containing products, including Tegretol® (Novartis Singapore Pte Ltd) and four other generic brands.

A strong association has been established between HLA-B*1502 allele and CBZ-induced SJS/TEN in Asian populations. Alternative antiepileptics are available, and genotyping for the allele was determined to be cost effective in Singapore.[1,2] Consequently, MOH, in a joint Dear Healthcare Professional Letter with HSA in April 2013, stated that genotyping for HLA-B*1502 is the standard of care prior to the initiation of CBZ therapy in new patients of Asian ancestry.[3]



CBZ-induced SCAR outcomes

From 2003 to 2012, HSA received an average of 15 reports of CBZ-induced SJS/TEN per year. Since April 2013, more than 2,700 patients have been genotyped for HLA-B*1502, of which 11% were found to carry the HLA-B*1502 allele. HSA has recently received one report of CBZ-induced SJS among all the patients screened for the allele. This suspected case of CBZ-induced SJS occurred in a patient who was genotyped negative. The patient developed SJS 32 days after the initiation of CBZ. A concomitant drug, gabapentin, was initiated 68 days prior to the reaction.

HLA-B*1502 has not been shown to be a risk predictor of CBZ-induced DRESS. HSA has received two reports of CBZ-induced DRESS in patients who were genotyped negative. CBZ was the only suspected drug in both cases. The time-to-onset was 31 and 44 days, respectively.

While genotyping for HLA-B*1502 has successfully mitigated the risk of CBZ-induced SJS/TEN locally, these three cases of CBZ-induced SCAR are a reminder of the need to remain vigilant for SCAR even among those who tested negative for HLA-B*1502 as non-genetic factors may be involved in the development of SCAR.

HSA's advisory

Genotyping for the HLA-B*1502 allele prior to the initiation of CBZ therapy in new patients of Asian ancestry is the standard of care in Singapore. HLA-B*1502 genotyping test has been proven to be highly effective in distinguishing high-risk patients from low-risk patients who are able to continue to use this cost-effective medicine.

Healthcare professionals are reminded of the following:

- HLA-B*1502 genotype testing specifically identifies patients at high risk of developing CBZ-induced SJS/TEN, but not CBZ-induced DRESS.
- HLA-B*1502 test results should be obtained prior to prescribing CBZ. This is because of the possibility of development and progression of SJS/TEN in susceptible patients even after prompt discontinuation of the drug.
- The use of CBZ should be avoided and treatment alternatives are strongly recommended in patients who are found to be positive for HLA-B*1502. As a precaution, these patients should also not be prescribed phenytoin, as there is preliminary data suggesting a suspected association between HLA-B*1502 and phenytoin-induced SJS/TEN.
- Genetic testing should not substitute for appropriate clinical vigilance and patient management. Although reported to be rare, patients who test negative for HLA-B*1502 may still be at risk of developing CBZ-induced SCAR, including DRESS. The role of other factors which may contribute to the development of SCAR in these patients, such as drug dose, concomitant medications and co-morbidities, have not been studied.
- Clinical vigilance for CBZ-induced SCAR including DRESS should continue, especially during the first 12 weeks following initiation of CBZ therapy.

Healthcare professionals are encouraged to report any suspected serious ADRs relating to CBZ use to the Vigilance and Compliance Branch.

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RESTRICTIONS ON THE USE OF CODEINE-CONTAINING PRODUCTS IN CHILDREN AND ADOLESCENTS

Key Points

- Reassessment of benefit-risk profile of codeine-containing products for pain relief and cough suppression confirmed the risk of respiratory depression in children and adolescents
- The licensed indication and minimum age of use of codeine-containing products will be restricted to the treatment of unproductive cough and acute moderate pain not relieved by analgesics in children, 12 years old and above
- Healthcare professionals are advised to take the recommendations into consideration when prescribing codeine-containing products

Background

HSA first issued an interim safety update in 2014 to healthcare professionals which summarised the overseas recommendations on the use of codeine-containing products for pain relief in paediatric patients. It also informed healthcare professionals that HSA would be conducting a comprehensive review of such products in Singapore for pain relief and for the relief of cough symptoms in children.[1] Subsequently, a Dear Healthcare Professional Letter was issued in July 2016 regarding new restrictions on the use of codeine-containing products in order to reduce the risk of death and respiratory depression in infants and children.[2] This article serves as a reminder on the restrictions for the use of codeine-containing products.

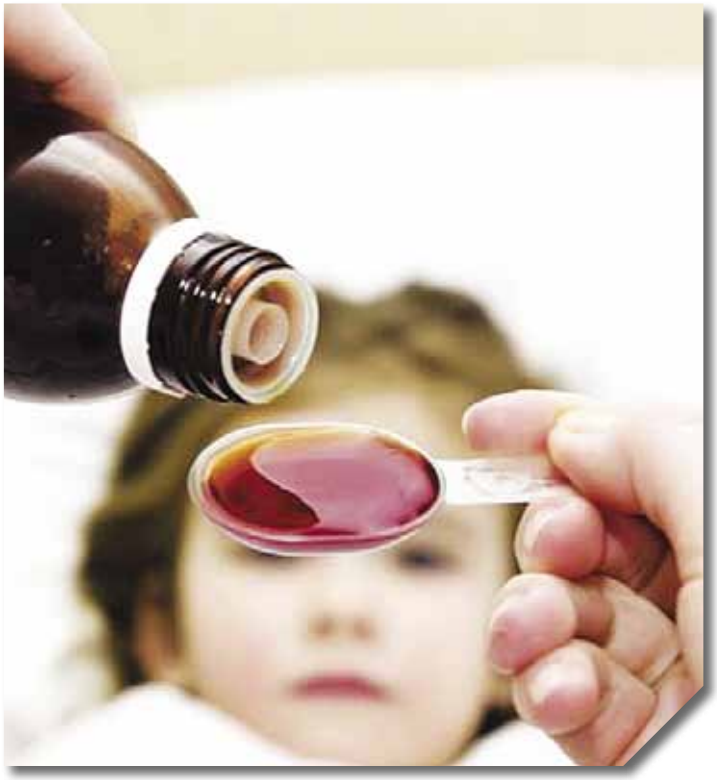
Codeine has been registered in Singapore since 1989 for the treatment of pain and the relief of cough and cold. Locally, there are seven codeine-containing products indicated for pain and 22 codeine-containing products indicated for the relief of cough and cold registered for use in children and adolescents. They are available in various dosage forms such as tablets, syrups and injections.

International regulatory actions

In February 2013, the US Food and Drug Administration (US FDA) issued its recommendation to contraindicate the use of codeine for postoperative pain management in children who have undergone tonsillectomy and/or adenoidectomy. The US FDA also strengthened the product information with warnings regarding deaths and respiratory depression, following a safety review of codeine. The review considered reports of deaths and respiratory depression in young children aged 2 to 5 years old who had received codeine following tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome.[3] It found that these children had evidence of being "ultra-rapid metabolisers" of substrates of CYP2D6, including codeine, and might have been particularly sensitive to the respiratory depressant effects of codeine, due to increased conversion of codeine to morphine, and especially as they already had underlying breathing problems. However, the contraindication applies to all children below 18 years old undergoing tonsillectomy and/or adenoidectomy because it is not easy to identify ultra-rapid metabolisers of codeine. In June 2013, the European Medicines Agency (EMA) contraindicated the use of codeine for postoperative pain management in children and adolescents below 18 years of age who have undergone tonsillectomy and/or adenoidectomy.[4]

In April 2015, following further review of the use of codeine-containing products for relief of cough and cold in children, the EMA contraindicated the use of codeine-containing products for cough and cold in children under 12 years old in view of the serious adverse events such as deaths and respiratory depression, and limited efficacy data in this age group.[5] Evaluation of the use of codeine-containing products for relief of cough and cold in children by the US FDA is still ongoing.[6]

In July 2016, Health Canada announced that codeine is contraindicated in patients under 18 years old for the treatment of post-surgical pain following tonsillectomy and adenoidectomy due to the increased risk of serious breathing problems. Codeine is already not recommended for children younger than 12 years old.[7]



HSA's benefit-risk assessment and advisory

To date, HSA has received five local reports of respiratory adverse events (AE) such as dyspnoea and bronchospasm in children between 9 to 16 years old associated with the use of codeine-containing cough products. No death or severe respiratory depression has been reported locally.

Taking into consideration the current available scientific evidence, input from local clinical experts, local and overseas AE reports, the potential for serious and fatal AEs in the local population and international regulatory actions, HSA has reviewed the benefits versus the risks of codeine and is recommending the following restrictions on the use of codeine-containing products in Singapore:

- Codeine is not recommended for the treatment of post-operative pain following surgical procedures such as tonsillectomy/ adenoidectomy in children and adolescents below 18 years old due to the increased risk of respiratory depression.

- For treatment of unproductive cough and treatment of acute moderate pain not relieved by analgesics, codeine remains indicated for those 12 years old and above. The lowest effective dose should be used for the shortest possible duration.

- Caution is advised when codeine is used in children with underlying respiratory conditions, including those with asthma and other chronic breathing problems.

- Parents and caregivers should be advised on the possible signs and symptoms of respiratory depression in their children, such as unusual sleepiness, confusion and difficult or noisy breathing, and to seek immediate medical attention if these are observed.

- Nursing mothers should also be advised to exercise caution when taking codeine, as codeine's metabolite (morphine) may subsequently be found in the breast milk. If the infant shows signs of increased sleepiness, difficulty when breastfeeding, breathing difficulties or limpness, immediate medical attention should be sought.

HSA is working with the companies of codeine-containing products to update their local package inserts with the new restrictions.

Healthcare professionals are encouraged to take into consideration the above recommendations when prescribing codeine. They are also encouraged to report any suspected serious AEs related to codeine to the Vigilance and Compliance Branch of HSA.

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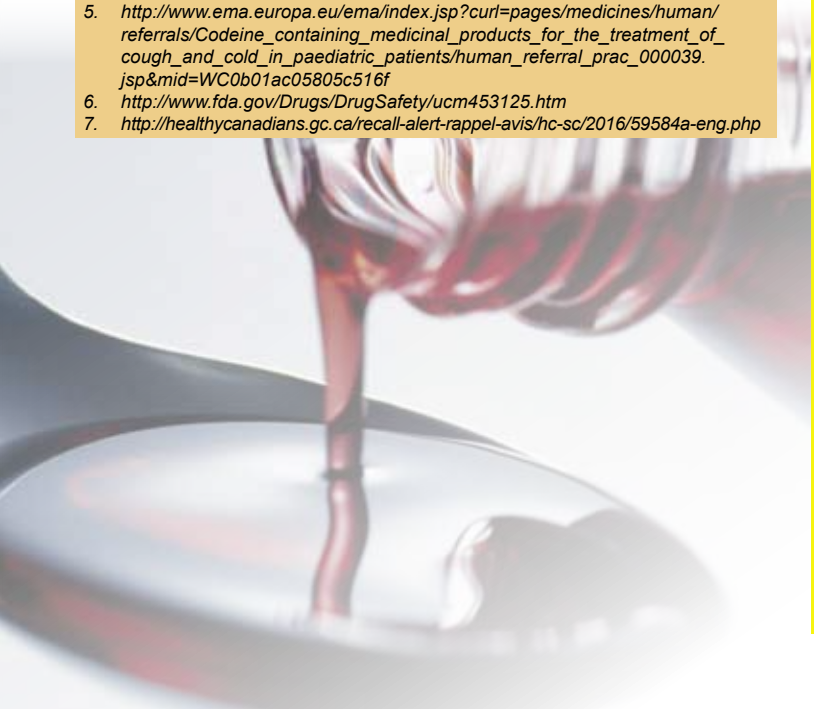

FLUOROQUINOLONES AND POTENTIAL RISK OF RETINAL DETACHMENT

Key Points

- Two large cohort studies have found a statistically significant increased risk of retinal detachment with use of oral fluoroquinolones. Based on the available data, a causal relationship between fluoroquinolones intake and retinal detachment cannot be ruled out
- Healthcare professionals are advised to consider this potential risk when prescribing and dispensing fluoroquinolones and recommend patients to seek immediate medical attention if they experience visual disturbances
- Symptoms include[1]:
  - Sensation of flashing light, often accompanied by showers of 'floaters'
  - Appearance of dark shadow in some parts of the vision
  - Blur central vision
  - Vision loss

HSA would like to highlight the potential risk of retinal detachment associated with the use of oral fluoroquinolones.

Fluoroquinolones are broad-spectrum antibiotics that are used to treat a wide range of indications such as the infections of the urinary tract, respiratory tract, skin and soft tissue, bones and joints, and abdominal cavity. Oral fluoroquinolones licensed locally include ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin, pefloxacin, ofloxacin, and lomefloxacin.

What is retinal detachment?

Retinal detachment refers to the separation of the inner layers of the retina from the underlying retinal pigment epithelium. The common initial symptoms include the sensation of a flashing light (photopsia) related to retinal traction, which is often accompanied by a shower of floaters and vision loss. Over time, the patient may report a shadow in the peripheral visual field, which, if ignored, may spread to involve the entire visual field in a matter of days. Vision loss may be described as cloudy, irregular, or curtain-like.[12]

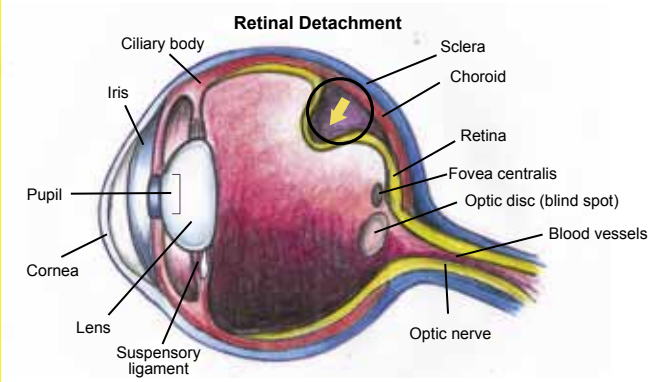

Figure 1: Image representation of retinal detachment (Image not drawn to scale)

Background

The association between oral fluoroquinolones intake and occurrence of retinal detachment has been investigated in several epidemiological studies. Two large cohort studies[2] have found a statistically significant increased risk of retinal detachment with use of oral fluoroquinolones.[3]

The first study was a nested case-control study involving a cohort of patients in British Columbia, Canada, who had visited an ophthalmologist between January 2000 and December 2007. Out of 989,591 patients, 4,384 cases of retinal detachment and 43,840 controls were identified. This study found the current use of oral fluoroquinolones to be associated with a higher risk of developing a retinal detachment (3.3% of cases vs 0.6% of controls; adjusted rate ratio (ARR), 4.50 (95% confidence interval [CI], 3.56-5.70]). For current users, the mean number of days from the first fluoroquinolone prescription to the first event of a retinal detachment was 4.8 ± 4.8 days. No risk was observed among recent users (ARR, 0.92; 95% CI, 0.45-1.87) or past users (ARR, 1.03; 95% CI, 0.89-1.19).

The second study was a retrospective population-based cohort study conducted with data extracted from the Taiwan National Health Insurance Research Database from 1998 to 2010. The rate of rhegmatogenous retinal detachment (RRD) in adults treated with an oral fluoroquinolone (n=178,179 prescriptions) was compared with adults treated with oral amoxicillin (n = 178,179 prescriptions). The overall adjusted hazard ratio for fluoroquinolones use and RRD was 2.07 (95% CI, 1.45-2.96). The interval between use of oral fluoroquinoloness and onset of RRD was 35.5 days (interquartile range, 14-57 days).

This increased risk of retinal detachment was not confirmed in other published studies[4,5,6,7,8] as well as in a study conducted by the European Medicines Agency (EMA).[9] However, in most of these studies, confidence intervals were relatively wide and thus a small increase in risk cannot be excluded.

Plausible mechanism for retinal detachment[2]

The exact mechanism of retinal detachment with fluoroquinolones is unknown. The retina is a delicate structure within the eye attached to the cortical vitreous by a complex matrix of collagen fibers. Vitreous liquefaction, a normal aging change of the vitreous, can result in retinal traction, which in turn can lead to retinal tears and subsequently retinal detachment. Conditions that interfere with connective tissue and collagen formation also increase vitreous liquefaction and have been shown to increase the risk of retinal detachment. Isolated animal studies have shown that fluoroquinolones interfere with collagen synthesis[10] and disrupt the extracellular matrix outside the retina, including the corneal matrix.[11] Hence it is postulated that fluoroquinolones could damage connective tissue including that of the vitreous and vitreous cortex through the aforementioned mechanisms observed in animals, potentially leading to retinal detachment.

International regulatory actions

The EMA and Health Canada (HC)[12] have reviewed this safety concern. Both agencies concluded that a causal relationship between fluoroquinolones intake and retinal detachment cannot be excluded based on the available data. Given the seriousness of retinal detachment with possible sequelae and the need for immediate intervention by an ophthalmologist in the event when this occurs, both EMA and HC have recommended the package inserts of fluoroquinolones to highlight the urgency to consult a healthcare professional if patients experienced vision problems during or following oral fluoroquinolone administration.

HSA's actions and advisory

HSA has not received any reports of retinal detachment associated with the use of fluoroquinolones although we have received several reports describing visual disturbances such as blurred vision, eye redness, itching and conjunctivitis.

HSA has been working with the companies to update the package inserts of fluoroquinolone-containing products registered in Singapore to warn of this potential risk and to highlight the need to seek medical attention in the event of visual impairment and disturbances. In view of the fact that retinal detachment is serious and that its association with oral fluoroquinolones use cannot be ruled out, healthcare professionals are advised to consider this potential risk when prescribing and dispensing fluoroquinolones to patients. Healthcare professionals are also encouraged to report any cases of retinal detachment associated with the use of fluoroquinolones to HSA.

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Useful Information

- Doctors, dentists and pharmacists can claim continuing education points for reading each issue of the HSA Adverse Drug Reaction News Bulletin.
- Doctors can apply for one non-core Continuing Medical Education (CME) point under category 3A, dentists can apply for one Continuing Professional Education (CPE) point under category 3A and pharmacists can apply for one patient-care Continuing Professional Education (CPE) point under category 3A per issue of the bulletin.

LIST OF DEAR HEALTHCARE PROFESSIONAL LETTERS ON SAFETY CONCERNS ISSUED BY HSA, PHARMACEUTICAL AND MEDICAL DEVICE COMPANIES (1 AUGUST 2016 TO 30 NOVEMBER 2016)

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

Therapeutic products

8 Aug 2016	**Adempas® (riociguat)** New contraindication for patients with pulmonary hypertension associated with idiopathic interstitial pneumonia
19 Oct 2016	**Domperidone-containing products** New recommendations on use due to the potential risk of serious cardiovascular events associated with its use
20 Oct 2016	**Actilyse® (alteplase) Treatment Set 50mg/vial** Reminder on the importance to follow the reconstitution process provided to prevent the rubber stopper from being pushed into the vial

Medical devices

4 Jul 2016*	**Ethicon Physiomesh™ Flexible Composite Mesh** Voluntary recall of all lots due to high incidence of recurrence and reoperation rates after laparoscopic ventral hernia repair using the affected product
29 Jul 2016*	**Locking Screws Stardrive® Ø 2.4 mm, self-tapping, length 12 mm, Titanium-Alloy-Niobium Alloy** Voluntary recall of selected lots due to potential breakage between the head and shaft of the affected product
10 Aug 2016	**TIGR® Matrix Surgical Mesh** Advisory not to use TIGR® Matrix Surgical Mesh for repair of direct inguinal hernia
12 Aug 2016	**Absorb™ and Absorb GT1™ Bioresorbable Vascular Scaffold Systems** Update to the reference vessel diameters in the indications for all sizes
12 Aug 2016	**HEALAFLOW® products** Update to the Instruction For Use on the proper handling of the syringe to avoid the dissociation of the finger grip from the body during injection
16 Aug 2016	**Microvention PHIL (Precipitating Hydrophobic Injectable Liquid) Non-Adhesive Liquid Embolic System** Voluntary recall of selected lots as the PHIL container (syringe) may elute unintended elements (metals) into the PHIL device formulation
18 Aug 2016	**ETHICON MERSILENE™ Tape** Notification on incorrect 'Instruction for Use' inserts supplied in selected products
1 Sep 2016	**Medtronic Deep Brain Stimulation Pocket Adaptor Models 64001 and 64002** Advisory on handling procedure as stated in the current labelling in the implant manual following recent reports of high impedances from returned product analysis
1 Sep 2016	**Graseby Syringe Drivers (Models MS16A and MS26)** Advisory on design limitations, which may cause incidents which include incorrect amounts of fluids being delivered and the device stopping during infusion
13 Sep 2016	**HeartWare® Ventricular Assist Device (HVAD) sterile implant kit** Voluntary recall of selected lots, including the HAVD pump, as they may be more susceptible to electrical faults if the driveline becomes contaminated
21 Sep 2016	**Misago® Self-Expanding Stent System** Voluntary recall as products were found not conforming with specifications defined in terms of stent diameter at proximal/distal ends after self-expansion, and/or the shape of the stent
27 Sep 2016	**BIOLOX® DELTA & BIOLOX® FORTE Hip Prostheses with ceramic components** Advisory on risk of ceramic fragments from fractured ceramic components of hip prostheses remaining in the joint during revision surgery, which can lead to premature wear in non-ceramic revision components
5 Oct 2016	**Boston Scientific Lotus™ Valve System** Voluntary recall of selected lots due to the potential for the release mandrel to break
13 Oct 2016	**LFIT™ Anatomic CoCr V40™ Femoral Heads** Voluntary recall of selected lots due to potential hazards from taper lock failure
27 Oct 2016	**St. Jude Medical Implantable Cardioverter Defibrillator and Cardiac Resynchronization Therapy Defibrillator** Voluntary recall of selected models due to risk of premature battery depletion
27 Oct 2016	**Restylane Lidocaine 1mL** Notice on incorrect Singapore-specific Instructions for Use supplied with specific batches
7 Nov 2016	**Perceval Sutureless Heart Valve** Labelling update to provide clarification to the implantation steps that is intended to assist healthcare professionals during implantation procedures
10 Nov 2016	**TANDEM™ Bipolar Hip System** Voluntary recall of selected models as a subset of Bipolar shells were manufactured with an out-of-specification retainer groove
16 Nov 2016	**Endologix Nellix® EndoVascular Aneurysm Sealing System** Update to the Instruction For Use due to potential risks of implant displacement, endoleaks, and/or aneurysm enlargement
22 Nov 2016	**Bard multi-length ureteral stents** Advisory regarding possible formation of knots in the stents which may result in injury to the ureter during removal and/or the need for additional surgical intervention

** Outstanding July DHCPLs not published in Sep 2016 issue*

IDELALISIB AND RISK OF SERIOUS INFECTIONS

Key Points

- A higher incidence of serious adverse events and increased risk of death, mainly due to infections, was observed in patients receiving idelalisib in combination with standard therapies in three Phase III clinical trials evaluating first-line CLL and relapsed iNHL
- It is recommended that all patients should receive prophylaxis for *Pneumocystis jirovecii* pneumonia throughout idelalisib treatment
- Healthcare professionals are advised to monitor for signs and symptoms of infection in patients who are prescribed idelalisib

HSA would like to inform healthcare professionals about the higher incidence of serious adverse events (AEs) and increased risk of death observed in patients receiving idelalisib in three Phase III clinical trials that were evaluating patient populations and/or treatment combinations which are not registered.

Idelalisib (Zydelig®, Gilead Sciences Singapore Pte Ltd) is a phosphatidylinositol 3-kinase inhibitor, registered locally in February 2016. It is approved, in combination with rituximab, for the treatment of relapsed chronic lymphocytic leukaemia (CLL) in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities. It is also indicated for the treatment of relapsed follicular B-cell non-Hodgkin lymphoma and relapsed small lymphocytic lymphoma in patients who have received at least two prior systemic therapies, based on overall response rates to idelalisib monotherapy.

Safety findings from clinical trials

The three Phase III clinical trials, where an increased rate of serious AEs, and increased mortality were detected, investigated the addition of idelalisib to standard therapies in first-line treatment of CLL and relapsed indolent non-Hodgkin lymphoma (iNHL). The clinical trial on CLL studied idelalisib for first-line treatment of CLL, which is not an approved use for idelasilib. The clinical trials on relapsed iNHL investigated patients with disease characteristics different from the currently approved indications or investigated idelalisib in treatment combination that is not currently approved for relapsed iNHL.

Gilead's review of the clinical trials found an increased risk of serious AEs, including deaths, in patients receiving idelalisib compared to placebo for first-line treatment of CLL and relapsed iNHL. The majority of events were infections, which included sepsis and opportunistic infections such as *Pneumocystis jirovecii* pneumonia (PJP) and cytomegalovirus (CMV) infections. These trials have since been terminated by the company.

Recommendations by European Medicines Agency (EMA)

In March 2016, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) initiated a safety review on idelalisib in response to the findings from the Phase III clinical trials.[1] In July 2016, PRAC concluded that the benefit-risk balance of idelalisib for its authorised use in the treatment of relapsed CLL and follicular lymphoma that is refractory to two prior lines of treatment remains positive.[2] Although the trials reviewed for this safety concern did not evaluate idelalisib in its currently authorised patient populations or treatment combinations, the committee considered that the risk of serious infections, including PJP, associated with idelalisib remained relevant to its authorised use. The recommendations by PRAC to minimise this risk included prophylaxis for PJP and regular blood count monitoring. PRAC also recommended that idelalisib should not be initiated in patients with any generalised infection.

Local situation and HSA's advisory

To date, HSA has not received any local reports of serious infections associated with the use of idelalisib. The local package insert of Zydelig® has been strengthened to include the following warnings:

- Idelalisib is not recommended for first-line treatment of CLL
- Prophylaxis for PJP should be administered to all patients throughout idelalisib treatment
- Monitor patients for CMV and discontinue idelalisib if there is evidence of infection or viraemia (positive PCR or antigen test)
- Monitor blood counts at least every two weeks for the first six months, and at least weekly in patients with neutrophil counts less than 1.0Gi/L

A Dear Healthcare Professional Letter was issued by the company in April 2016 to communicate the safety concerns to healthcare professionals.[3]

Healthcare professionals are advised to take into consideration the above safety information when prescribing idelalisib and to monitor their patients for signs and symptoms of infections throughout idelalisib treatment.

References

1. *http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Zydelig_20/Procedure_started/WC500203478.pdf*
2. *http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Zydelig/human_referral_prac_000055jsp&mid=WC0b01ac05805c516f*
3. *http://www.hsa.gov.sg/DHCPL*

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