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SAFETY REVIEW ON RISK OF SERIOUS ALLERGIC REACTIONS WITH CHLORHEXIDINE

Key Points

- ❖ Chlorhexidine is known to induce rare cases of hypersensitivity, including generalised allergic reactions and anaphylactic shock
- ❖ Chlorhexidine-containing products should not be administered to patients with a documented or suspected history of chlorhexidine allergy. The labels and instructions for use should be checked to establish if the products contain chlorhexidine prior to use on patients with a known allergy
- ❖ Although the prevalence of chlorhexidine hypersensitivity is likely to be rare, healthcare professionals should remain vigilant to the potential risk of serious allergic reactions, including anaphylaxis



HSA would like to inform healthcare professionals about the outcome of its review on the known risk of allergic reactions, including anaphylactic reactions, with chlorhexidine-containing products. This review was conducted following recent international safety alerts regarding serious allergic reactions reported with antiseptic products containing chlorhexidine. HSA's review of our local adverse event (AE) database did not identify any significant local signals with respect to serious allergic reactions associated with the use of chlorhexidine-containing products at this point in time. Healthcare professionals are encouraged to remain vigilant to this potential risk as such reactions could become life-threatening if not managed promptly.

Background

Chlorhexidine is a broad-spectrum antiseptic which is effective against Gram-positive and Gram-negative bacteria on the skin and is widely used to reduce the risk of bacterial infection. Chlorhexidine is present in a variety of topical and oromucosal antiseptic preparations in the form of creams, wipes, cleansers, mouthwashes, dental implants, contact lens solutions, lozenges, topical anaesthetic medicines and antimicrobial dressings. Some indwelling catheters such as urinary catheters and central venous catheters may also be coated or impregnated with chlorhexidine to prevent catheter-related infections.

International regulatory actions

(a) US Food & Drug Administration (US FDA)¹

In February 2017, US FDA issued a safety communication regarding serious allergic reactions with skin antiseptic products containing chlorhexidine gluconate. Although rare, US FDA shared that the number of AE reports of serious allergic reactions to these products had increased over the last five decades and recommended that the product labels for over-the-counter (OTC) chlorhexidine gluconate-containing products be updated with a warning about the possibility of serious allergic reactions. This warning is currently present in the US labelling for prescription chlorhexidine gluconate mouthwashes for treatment of gingivitis and prescription oral chips used for periodontal disease.

US FDA identified 43 worldwide serious cases of anaphylactic reactions with the use of topical chlorhexidine gluconate-containing products. These cases were reported to the FDA Adverse Event Reporting System (FAERS) between January 1969 and June 2015, of which 24 cases (56%) were reported after 2010. Serious outcomes were reported and these include life-threatening conditions (26 cases), hospitalisation (12 cases) and death attributed to anaphylactic reaction (2 cases). All reported cases had a positive temporal association to the use of chlorhexidine gluconate-containing products, with seven cases reporting a positive allergy rechallenge. An additional nine cases of anaphylactic reaction associated with chlorhexidine were identified from medical literature and the National Electronic Injury Surveillance System: Cooperative Adverse Drug Event Surveillance (NEISS-CADES) database.

(b) Health Canada²

Health Canada issued a safety communication in May 2016 on the risk of serious hypersensitivity reactions with the use of non-prescription topical chlorhexidine antiseptics. Its safety review took into account 53 domestic reports of serious allergic reactions with the use of non-prescription topical chlorhexidine-containing products, including three anaphylactic reactions, as well as published cases in medical





literature. Health Canada concluded that although uncommon, some conditions may increase the risk of anaphylaxis, such as using chlorhexidine in the mouth, on open wounds, or immediately before or during surgery. As such, Health Canada recommended updating the product information of non-prescription chlorhexidine-containing products with these new findings.

(c) Other regulatory agencies³⁻⁷

The Australian Therapeutic Goods Administration (TGA), UK Medicines & Healthcare Products Regulatory Agency (MHRA) and New Zealand Medicines and Medical Devices Safety Authority (Medsafe) also issued similar safety alerts between 2009 and 2013. The agencies informed healthcare professionals about the risk of serious hypersensitivity reactions with chlorhexidine-containing products, including topical anaesthetic gel and chlorhexidine-impregnated central venous catheters. They also reminded healthcare professionals that chlorhexidine is known to induce hypersensitivity, and that an alternative product should be used if they suspected a patient had an allergy to chlorhexidine. The labels and instructions for use should be checked to establish if the products or devices contain chlorhexidine prior to use on patients with a known allergy.

HSA's review outcomes

HSA's current review of local AE reports concluded that there was no significant increase in the total number of AE reports associated with chlorhexidine hypersensitivity received by HSA over the past years. The majority of reports described non-serious AEs such as pruritus and rash. Fifteen reports of anaphylactic reactions related to chlorhexidine (route of administration was reported as topical for two cases and not listed for the rest) were identified over a span of 36 years (1981 to 2017). No increasing trend of serious allergic reactions to chlorhexidine-containing products across the years was observed. HSA's review did not identify any significant local safety signals regarding serious allergic reactions with the use of chlorhexidine at this point in time. Understandably, there may possibly be some cases of chlorhexidine-induced serious allergic reactions that might have gone unreported as the causality to the offending agent might not be apparent. Nevertheless, HSA will continue to monitor this safety concern and will take appropriate and timely action if further risk mitigation measures are deemed necessary.

HSA's advisory

Chlorhexidine is known to induce hypersensitivity, including generalised allergic reactions and anaphylactic shock. Although the prevalence of chlorhexidine hypersensitivity is likely to be rare, healthcare professionals are advised to remain vigilant to the potential risk of serious allergic reactions, including anaphylaxis, with chlorhexidine-containing products. The product labels or instructions for use should be checked to establish if the products contain chlorhexidine prior to use on patients with a documented or suspected history of an allergic reaction to chlorhexidine. Healthcare professionals are advised to inform their patients to stop using the product and seek immediate medical attention if they experience symptoms of a serious allergic reaction, such as wheezing, swelling of the face, or severe rashes.

COMMONLY ENCOUNTERED CATEGORIES OF ADULTERATED HEALTH PRODUCTS

Key Points

- Healthcare professionals (HCPs) are encouraged to look out for AEs arising from the use of adulterated complementary health products (CHPs)
- HCPs are encouraged to ask their patients about the use of CHPs when taking their medication history
- HCPs are advised to take into consideration some of the common signs of potential dubious/adulterated products in their assessment of AEs

From January 2014 to June 2017, HSA received 40 adverse event (AE) reports from HCPs associated with adulterated health products* sold under the guise of CHPs. The AEs included Cushing's syndrome, worsening of underlying medical conditions (e.g., diabetes, hypertension), drug-induced liver injuries, hallucinations, dyspnoea and tachycardia. More than half of these reports involved CHPs taken for pain relief, slimming and general well-being.

Common marketed claims of adulterated health products

Two of the common marketed claims of adulterated health products encountered through AE reports are highlighted below:

a) Pain relief

With an increasing life expectancy and an aging population in Singapore,¹ the prevalence of chronic pain is on the rise.² Pain management is an important concern for the elderly as it affects their quality of life.² HSA has received a number of AE reports of patients who had unwittingly consumed dubious/adulterated health products, which were marketed as CHPs. Patients shared that these products were recommended by well-meaning friends/relatives or they had purchased them when they were travelling overseas. Exposure to unlabelled potent western ingredients may cause harmful effects and this is especially pertinent to those with underlying health issues and/or a history of drug allergies. Some of these products, claimed to relieve pain, had raised the suspicion of astute doctors. These products include 'LifeSparks 100% Natural Pain Relief Supplement', 'Herba Qaseh 1001 Khasiat Penawar' and 'JC Gold'. Some of the common observations in patients taking such products include:

- Rapid pain relief (unexpected therapeutic efficacy due to potent western ingredients)
- Symptoms associated with Cushing's syndrome (due to adulteration with steroids)
- Withdrawal symptoms e.g., malaise, confusion and hypotension.

b) Slimming

In the recent years, HSA has issued a number of press releases for adulterated slimming products sold via the online platform. These products often claim to contain all natural ingredients with little or no AEs. Contrary to these claims, some of these products were tested and found to be adulterated with sibutramine or its analogue(s). Examples of such products include '1 Day Diet', 'Anyang Herbal Blue', 'Nutriline Bluvelle' and 'Nutri Drops Grapefruit Diet'. The amount of sibutramine found in some of these products had exceeded the maximum recommended therapeutic dose of sibutramine of 15mg. In one particular product, 'Anyang Herbal Blue', the dosing instruction on the product label was eight times the maximum recommended dose for sibutramine.

References

- <https://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm539575.htm>
- <https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/safety-reviews/summary-safety-review-topical-antiseptic-non-prescription-chlorhexidine-products-potential-risk.html>
- <https://www.tga.gov.au/publication-issue/australian-adverse-drug-reactions-bulletin-vol-28-no-2>
- <https://www.tga.gov.au/publication-issue/medicines-safety-update-volume-3-number-3-june-2012>
- <https://www.gov.uk/drug-safety-update/chlorhexidine-reminder-of-potential-for-hypersensitivity>
- <https://www.gov.uk/drug-device-alerts/medical-device-alert-all-medical-devices-and-medicinal-products-containing-chlorhexidine-risk-of-anaphylactic-reaction-due-to-chlorhexidine-allergy>
- <http://medsafe.govt.nz/profs/PUArticles/June2013Chlorhexidine.htm>

Local case reports

We highlight two AE cases that were reported to HSA in 2016 involving health products that were found to contain undeclared potent western ingredients.

a) Case report 1: 'LifeSparks 100% Natural Pain Relief Supplement' marketed for pain relief

A male patient in his 60s took 'LifeSparks 100% Natural Pain Relief Supplement' for leg pain and gout and 'LONGRED Oyster-x' to prevent prostate problems. He experienced rapid pain relief but developed severe gastric pain and facial swelling.

The label of 'LifeSparks 100% Natural Pain Relief Supplement' included medicinal claims that it "relieves gout, arthritis and aching joints". Laboratory tests detected chlorpheniramine, dexamethasone, diclofenac, paracetamol, piroxicam and sulphamethoxazole in 'LifeSparks 100% Natural Pain Relief Supplement' and an analogue of sildenafil in 'LONGRED Oyster-x'.



b) Case report 2: '1 Day Diet' marketed for slimming

A female patient in her 30s experienced dyspnoea, tachycardia and sweaty palms after consuming '1 Day Diet' for two weeks. The product was purchased online and labelled to be a "100% pure natural" slimming product with "quick effect". Laboratory tests detected sibutramine in the patient's sample of these products.



Common signs of dubious/adulterated health products

Based on the case reports of adulterated health products received by HSA, some of the signs of a dubious/adulterated product include:

- Medicinal claims or exaggerated claims on the effects of the product
- Misspelled words and use of poor grammar on the packaging
- Lack of batch number and/or expiry date
- Lack of information with regard to the manufacturer and/or distributor
- False claims that product is approved by HSA (import and sale of health supplements and traditional medicines in Singapore do not require prior approval from HSA)

With the advancement in technology, some adulterated products may be packaged professionally that it appears exactly like the legitimate products.

HSA's advisory

Given the increasing trend of consumers turning to the use of CHPs and the wider usage of e-commerce for the purchase of these products, HCPs are encouraged to ask their patients about the use of CHPs when taking medication history. This information may be useful for the differential diagnosis of adverse events experienced by their patients. HCPs can also help to reinforce the message to patients that they should be wary of consuming health products with exaggerated claims. HCPs are also encouraged to stay vigilant and report any AEs suspected with the use of adulterated health products to the Vigilance and Compliance Branch of HSA.

References

1. <https://www.nptd.gov.sg/PORTALS/0/HOMEPAGE/HIGHLIGHTS/population-in-brief-2016.pdf>
2. *Ann Acad Med Singapore*. 2009; 38: 937-42

* A health product is adulterated if it contains any substance or ingredient that is not stated on its label as being one of its constituent substances or ingredients. However, inactive ingredients need not be labelled as long as they are permitted as food additives or flavouring agents according to the Codex Alimentarius or such other similar document(s) which are approved by Health Sciences Authority (HSA).

Regulation of complementary health products (CHPs) in Singapore

HSA applies a risk-based approach in the regulation of different categories of health products. Risk is determined by factors such as product ingredients, presentation and methods of use and claims.

Therapeutic products are regulated more stringently as they contain potent active ingredients. Complementary health products (CHPs) including Chinese Proprietary Medicines (CPM), traditional medicines (TM), and health supplements (HS), generally contain less potent ingredients, and hence are subjected to a lighter-touch regulation.

CPM are products containing ingredients that are documented in stipulated traditional medicine references that are internationally regarded and used according to the TCM system of therapeutics. All CPM dealers must be licensed by HSA and must apply for product listing approval for each of the CPM before they can import, manufacture and/or sell the products in Singapore. Dealers have the responsibility to ensure that their CPM meet relevant safety and quality requirements, including compliance with stipulated limits on toxic heavy metals and microbial contents.

TM, in the local context refers to Malay and Indian traditional medicinal products, whilst HS are products that generally contain ingredients such as vitamins, minerals or substances derived from natural sources. TM and HS are currently not subjected to pre-market approval nor do they require approval for their manufacture, importation and sale.

The importers, wholesale dealers, manufacturers and sellers of TM and HS are responsible for the safety and quality of their products. This includes ensuring the absence of prohibited substances such as western medicinal ingredients e.g. steroids and compliance with stipulated limits on toxic heavy metals. In addition, as HS are not intended to diagnose, treat, cure or prevent any disease, dealers of HS must also ensure that their product labels and advertisements do not make such claims.

Although TM and HS are not subjected to pre-market approval, HSA has in place a post-market surveillance programme to monitor the safety of health products so as to initiate timely product recalls when necessary. This includes adverse event monitoring and risk-based surveillance to sample products in the market to test for undeclared potent medicinal ingredients and harmful substances such as toxic heavy metals. Any product found to be unsafe would be withdrawn from the market.



USE OF RISK MANAGEMENT PLANS TO MANAGE SAFETY CONCERNS ASSOCIATED WITH THERAPEUTIC PRODUCTS

Key Points

- A Risk Management Plan is a company-developed document that details the important safety concerns associated with a therapeutic product* and the proposed activities to be implemented to monitor and manage these safety concerns post-approval.
- The requirement for companies to implement Risk Management Plans under the direction of HSA has been legislated in the Health Product (Therapeutic Products) Regulations since November 2016.
- An example of a risk minimisation activity is the development of educational materials for physicians and/or patients. HSA encourages healthcare professionals to utilise HSA-approved educational materials to support them in making informed decisions and in counselling their patients.



HSA has recently legislated its requirements for Risk Management Plans (RMPs) as part of its product lifecycle approach in the management of safety concerns associated with therapeutic products. Under the Health Product (Therapeutic Products) Regulations enacted in November 2016, companies may be required to implement RMPs under the direction of HSA to help ensure the benefits of therapeutic products outweigh their risks. This article aims to raise the awareness of healthcare professionals to RMPs, as well as provide some examples of risk minimisation activities that have been implemented locally to manage the safety concerns of therapeutic products post-approval.

Risk Management Plan

A RMP is a document developed by companies that details the important safety concerns associated with a therapeutic product and the proposed activities to be implemented to monitor and manage them post-approval. It serves as an important tool for

managing significant risks associated with a therapeutic product, and may involve the implementation of risk minimisation activities beyond product labelling and routine adverse event (AE) reporting to ensure the benefits of the product outweigh its risks.

RMP submission is mandatory for all new chemical/biological entities or biosimilar products submitted to HSA for product registration. They may also be requested by HSA for other therapeutic products on a case-by-case basis (e.g., products with new significant safety issues identified pre- or post-market).

Examples of risk minimisation activities in RMPs are:

- Development of educational materials (Physician Education Material and/or Patient Medication Guide)
- Implementation of a restricted access programme
- Implementation of a pregnancy prevention programme

Risk Minimisation Activities

(a) Educational materials for physicians and/or patients

HSA may request companies to develop educational materials for physicians and/or patients to inform them about pertinent safety concerns associated with a therapeutic product.

A Physician Educational Material (PEM), which is targeted at physicians and healthcare professionals, serves to complement the package insert by highlighting selected safety concerns of significance. It may also include recommendations on regular monitoring parameters and/or laboratory testing, information on monitoring of early signs of AEs that could require discontinuation or modification of patient therapy, or specific advisories related to the use of the product.

Similarly, a Patient Medication Guide (PMG), which comes in the form of booklets, handouts or patient alert cards, serves as a useful guide to remind patients on the risks associated with their medications and educate them on the steps they can take to minimise these risks. The PMG may highlight possible early signs of AEs, which allows patients to self-monitor and know when to seek medical attention. The PMG may also provide information on significant food-drug interactions so that patients are aware and can make the necessary dietary modifications to avoid these interactions.

PEMs and PMGs are reviewed and approved by HSA before dissemination to healthcare professionals and their patients. During the review process, HSA ensures that the educational materials are objective, free from promotional content and have adequately addressed the important safety concerns. In addition, should new safety issues emerge, HSA may require these materials to be updated or request for new materials to be developed as part of its ongoing post-market benefit-risk review. Healthcare professionals can identify HSA-approved educational materials by the statement "This document has been approved by HSA on [Date]" printed on them. The inclusion of this statement is a recent initiative started in the second half of 2016, in response to feedback from healthcare professionals regarding the difficulties in differentiating between promotional materials produced by companies and educational materials requested by HSA. Healthcare professionals are encouraged to utilise these educational resources to support them in making informed decisions and as an aid in counselling their patients.

Table 1 lists the products with educational materials approved by HSA to date.

* Therapeutic products comprise of western pharmaceutical products used for health-related medicinal purposes in humans. They are registered with HSA to ensure that they meet the appropriate standards of safety, quality and efficacy.

(b) Restricted access programme (RAP)

HSA may request for a RAP to be implemented for therapeutic products that are associated with significant safety issues that affect their overall benefit-risk profile, but have been assessed to remain beneficial for a selected group of patients with no suitable therapeutic alternatives. Under the RAP, risk mitigation measures such as a letter of undertaking by physicians and pharmacists to indicate their awareness of the risks, informed consent from patients that they have understood the risks, and the restriction of supply of product only to healthcare professionals enrolled in the RAP are put in place. Currently, there are two products placed under the RAP, namely aprotinin (Trasylol®) and tegaserod (Zelmac®).

(c) Pregnancy prevention programme (PPP)

HSA may also request for therapeutic products associated with teratogenicity to be placed under a PPP. The PPP comprises a number of components that collectively aims to minimise foetal exposure to the product. These components include i) patient counselling; ii) educational materials to inform healthcare professionals and patients about the risks of birth defects; iii) restricting the distribution of the product to physicians and pharmacies registered with the programme; and iv) signed acknowledgement by prescribers and patients confirming their understanding of the risks associated with foetal exposure of the product. For example, women of child-bearing potential would be required to acknowledge the need for effective contraception and mandatory pregnancy testing before, during and after treatment. Men would be required to use condoms during and after treatment if their partner is pregnant or of child-bearing potential and not using effective contraception.

To date, three products have been placed under the PPP, namely isotretinoin, lenalidomide (Revlimid®) and pomalidomide (Pomalyst®).

Conclusion

HSA looks forward to a close partnership with our healthcare professionals in the successful implementation of RMPs. We would also like to thank healthcare professionals for their strong support for the national AE reporting programme as we work together to protect public health.

Table 1. List of products with educational materials approved by HSA

Product	Active ingredient	Product	Active ingredient
Benlysta*	Belimumab	Pradaxa	Dabigatran
Blincyto	Blinatumomab	Priligy	Dapoxetine
Bortezomib-Actavis [^]	Bortezomib	Proart	Bosentan
Botox	Clostridium Botulinum Toxin Type A	Protos*	Strontium ranelate
Darzalex	Daratumumab	Revlimid	Lenalidomide
Dengvaxia	CYD Dengue virus serotype 1-4	Revolade	Eltrombopag
Effient [^]	Prasugrel	Romiplate	Romiplostim
Entyvio*	Vedolizumab	Scitropin A	Recombinant somatropin
Evoltra	Clofarabine	Soliris	Eculizumab
Exjade	Deferasirox	Tarceva	Erlotinib
Folotylin	Pralatrexate	Tracleer	Bosentan
Gilenya	Fingolimod	Tysabri	Natalizumab
Jadenu	Deferasirox	Valdoxan	Agomelatine
Kadcyla [^]	Trastuzumab emtansine	Vectibix [^]	Panitumumab
Keytruda*	Pembrolizumab	Velcade [^]	Bortezomib
Lemtrada	Alemtuzumab	Victrelis [^]	Boceprevir
Multaq	Dronedarone	Volibris	Ambrisentan
Nivestim [^]	Filgrastim	Xarelto*	Rivaroxaban
Nplate	Romiplostim	Yervoy	Ipilimumab
Opdivo*	Nivolumab	Zarzio [^]	Filgrastim
Opsumit	Macitentan	Zydelig*	Idelalisib
Pomalyst	Pomalidomide		

[^] only PEM available * only PMG available

AE CASE IN FOCUS: TEST YOURSELF

A Chinese male patient in his 50s diagnosed with metastatic rectal and colon carcinoma was prescribed chemotherapy with oxaliplatin and capecitabine. He was also prescribed three days of oral dexamethasone for each cycle of chemotherapy as prophylaxis against delayed chemotherapy-induced nausea and vomiting. His medical history included hypertension, hyperlipidaemia and chronic low back pain.

After receiving three cycles of chemotherapy, he experienced unilateral visual disturbances, seeing a vision of dark translucent circle with shiny dots inside the circle for a week. No other metamorphopsia or pain was experienced. After an eye examination and a macular optical coherence tomography scan, he was diagnosed with central serous chorioretinopathy (CSCR).

Question:

What could have caused CSCR in this patient?

HSA would like to thank Dr Ang Xin Hui and Dr Manish Kumar Sinha from the Department of Ophthalmology, Ng Teng Fong General Hospital and Dr Nesaretnam Barr Kumarakulasinghe from the Department of Haematology & Oncology, National University Cancer Institute, Singapore for their contributions to this article.

Answers can be found on page 6-7



LIST OF DEAR HEALTHCARE PROFESSIONAL LETTERS ON SAFETY CONCERNS ISSUED BY HSA, PHARMACEUTICAL AND MEDICAL DEVICE COMPANIES (1 MAY 2017 TO 31 AUG 2017)

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

Therapeutic products

14 Jun 2017	KEYTRUDA® (pembrolizumab) Risk of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis
21 Jul 2017	XGEVA® (denosumab) Solution for Injection 120mg/vial Risk of Multiple Vertebral Fractures that may occur following discontinuation of treatment, particularly in patients with risk factors such as osteoporosis or prior fractures

Medical devices

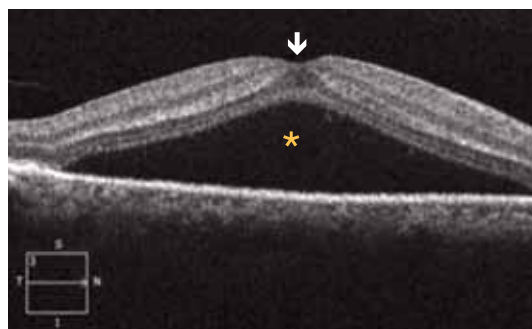
3 May 2017	AMO Healon Ophthalmic Viscosurgical Devices Voluntary recall of specific lots due to remote possible presence of microscopic glass particles
18 May 2017	Synthes MatrixMIDFACE, Synthes MatrixMANDIBLE, Synthes MatrixORTHOGNATHIC Voluntary recall of specific lots due to discrepancy between the length of screw etched on the clip and the actual screw length
22 May 2017	Thoratec® HeartMate II® LVAS Pocket System Controller Medical device correction due to reports of serious injuries and deaths associated with patient's attempts to exchange the primary System Controller to backup System Controller
25 May 2017	Medtronic Model 8637 SynchroMed® II Implantable Drug Infusion Pumps Update on failure rate of affected device due to reduced battery performance and to reinforce the previously communicated patient management recommendations
19 Jun 2017	Zimmer Biomet Knee, Hip and Nail implants Voluntary recall of selected lots due to packaging design verification test failures
28 Jun 2017	HeartMate III™ Left Ventricular Assist System Medical device correction due to communication error reports between the System Controller and the pump
4 Jul 2017	Cementless Oxford Partial Knee Unicompartamental Knee Replacement System Trend in reported tibial plateau fractures involving affected device and the importance of adhering to applicable surgical technique and appropriate sections in the Instruction for Use
20 Jul 2017	Zenith Alpha™ Thoracic Endovascular Graft Voluntary recall of selected sizes due to removal of indication for use in blunt thoracic aortic injury (BTAI) following additional complaints of graft thrombosis/occlusion when the product was used to treat BTAI
24 Jul 2017	Boston Scientific S-ICD (SQ-RX S-ICD Model 1010, EMBLEM™ S-ICD Model A209 and EMBLEM™ MRI S-ICD Model A219) Memory corruption advisory following an incident that led to atypical energy delivery preventing S-ICD arrhythmia detection/treatment

ANSWERS TO AE CASE IN FOCUS: TEST YOURSELF

The central serous chorioretinopathy (CSCR) was diagnosed as likely steroid-induced based on a history of steroid use and ophthalmoscopic findings. There was a history of seeing a partial central scotoma described as a dark translucent circle in the centre of the patient's vision which was suggestive of a macular lesion. Examination of his fundus using a slit lamp revealed a round serous detachment at the macula, without haemorrhage or any sign of inflammation elsewhere in the eye. The diagnosis was confirmed on macular optical coherence tomography which demonstrated the presence of the subretinal fluid.

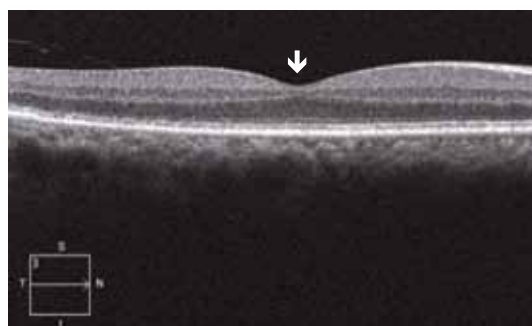
Upon diagnosis of CSCR, dexamethasone was stopped and alternative anti-emetics were prescribed. Repeated eye examination showed that CSCR resolved with discontinuation of steroids and no other treatment was given. Chemotherapy continued with no further deterioration in vision.

Repeated eye examination showed that CSCR had resolved which indicated a positive dechallenge. Another possible contributing factor include possible stress due to ongoing systemic chemotherapy. The patient also had a similar episode of CSCR several years ago which self-resolved with no treatment given. It has been reported in literature that glucocorticosteroid treatment may induce the recurrence of CSCR in patients who had previously developed an episode of CSCR independent of glucocorticoid use.¹



On initial presentation:

Macular optical coherence tomography of the patient's right eye fovea (white arrowhead). The dome-shaped dark hyporefective area (yellow asterisk) shows a serous detachment.



Six weeks after stopping dexamethasone:

Macular optical coherence tomography of the patient's right eye fovea (white arrowhead) showing resolution of the serous detachment.

About CSCR

CSCR is a disorder characterised by serous retinal detachment and/or retinal pigment epithelium detachment. These changes are usually confined to the macula but may be multifocal and more widespread.² CSCR typically affects men more commonly than women, but when related to exposure of exogenous glucocorticosteroids, has a less prominent gender predisposition and presents more often bilaterally, with atypical presentations such as chronic CSCR, acute bullous retinal detachment etc.¹

CSCR can occur in an acute or chronic form and risk factors for CSCR include genetic predisposition, cardiovascular diseases and hypertension, use of corticosteroids or sympathomimetic drugs, endocrine changes (i.e., pregnancy, stress), type A personality (behavioural traits include being competitive, ambitious, aggressive, impatient³ and more prone to stress) gastroesophageal disorders and sleep disturbances.⁴ Some traditional Chinese medicine and herbal medicine, especially those containing ginseng, may worsen the condition.⁵

CSCR is typically a self-limiting disease and visual recovery usually occurs within a few weeks to months without treatment. Several therapies such as laser photocoagulation and photodynamic therapy with verteporfin have been used for chronic and recurrent CSCR.

Use of corticosteroids associated with CSCR

The pathophysiology of corticosteroid-induced CSCR involves the mineralocorticoid receptors that are found on choroid blood vessels which have high affinity for glucocorticoids. The binding of glucocorticosteroids to these receptors increases the permeability of the choroid and induces small breaks in the retinal pigment epithelium, allowing choroid fluid to accumulate beneath the retina.⁶

Corticosteroids are used via various routes of administration. A wide range of dosages have been used in patients reported to have developed CSCR and may occur even at low doses. The latency of CSCR can range from few days to several years after initiation of treatment.¹

Local reports

To date, HSA has received three reports of CSCR associated with the use of corticosteroids. Other than the case study above, the other two cases reported involved a female in her 50s and male in his 70s who were given prednisolone and hydrocortisone respectively. The male patient had contact dermatitis where he had symptoms of rash over hand (mild erythema with vesicles and erosions over the dorsum of the bilateral hand) for 2 weeks and was given hydrocortisone cream to be applied twice daily for a week before he developed CSCR. Limited information was reported for the female patient and no further information was obtained upon follow-up.

Literature findings

The use of corticosteroids associated with CSCR is not new as there have been several reports in literature of CSCR associated with the use of corticosteroids as early as in the 1960s.¹ The possibility of such a relationship was more clearly indicated in the 1980s when several cases were presented and reviewed describing CSCR occurrence during glucocorticoid treatment.⁷ The prevalence of exogenous administration of glucocorticoid in patients developing CSCR has been reported at less than 10% in retrospective studies.^{8,9}

HSA's advisory

Corticosteroids are a class of immunosuppressant drugs that are widely prescribed for various medical conditions. Healthcare professionals should be aware that CSCR may develop or recur with exogenous corticosteroid administration at low doses and by any route and patients should be questioned on all forms of steroids that might be overlooked. If patient develops CSCR which is likely induced by corticosteroids, healthcare professionals are advised to discontinue the offending drug and consider other alternatives. Patients' symptoms should be monitored closely to prevent progression to chronic CSCR which if left untreated, may develop permanent moderate to severe visual acuity loss and decreased light sensitivity depending on the degree of photoreceptors outer segments damage.⁴

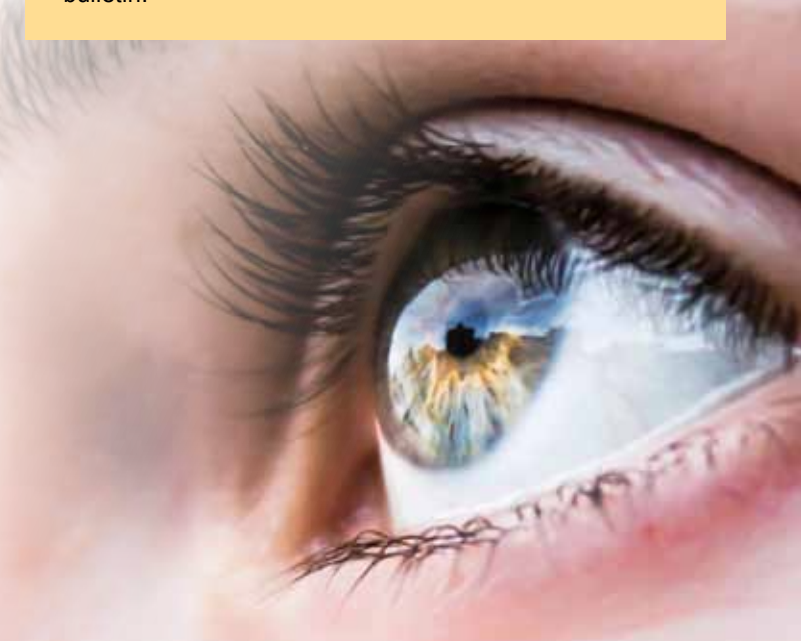
Healthcare professionals are advised to closely monitor patients on corticosteroids and to report any adverse events suspected to be associated with corticosteroids to the Vigilance and Compliance Branch of HSA. Your support towards the national adverse event monitoring programme is invaluable in safeguarding public health.

References

1. *Surv Ophthalmol* 2002 Sep-Oct; 47(5): 431-48
2. *Choroidal Disorders* 2017 p139-59
3. <https://www.simplypsychology.org/personality-a.html>
4. *Prog Retin Eye Res* 2015 Sep; 48: 82-118
5. <https://www.shec.com.sg/eye-conditions-and-treatments/common-eye-conditions-and-procedures/Pages/central-serous-chorioretinopathy.aspx>
6. *Joint Bone Spine* 2017 Feb 17
7. *Br J Ophthalmol* 1984 May; 68: 329-31
8. *Am J Ophthalmol* 1999 Jul; 128: 63-8
9. *Clin Ophthalmol* 2008;2: 199-201

USEFUL INFORMATION

Doctors, dentists and pharmacists can claim continuing education points for reading each issue of the HSA ADR 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.





REGULATORY UPDATES

DE-REGISTRATION OF LYSOZYME-CONTAINING PRODUCTS AS THERAPEUTIC PRODUCTS

HSA would like to update healthcare professionals on the de-registration of lysozyme-containing products as therapeutic products in Singapore. Therapeutic products comprise western pharmaceutical products and are registered with HSA to ensure that they meet the appropriate standards of safety, quality and efficacy. Currently, lysozyme-containing products are approved as an expectorant and mucolytic for chronic sinusitis, as well as treatment for bleeding. The affected products are Neuzym® (Eisai (Singapore) Pte Ltd), Leftose (Wellchem Pharmaceuticals Pte Ltd), Neuflo (Yung Shin Pharmaceutical (Singapore) Pte Ltd) and Lyzyme (Zyfas Medical Co).

Background

HSA has conducted a re-evaluation of the benefit-risk profile of lysozyme, which was first approved in 1989 as an expectorant and

mucolytic for chronic sinusitis and treatment for bleeding. The re-evaluation was undertaken following the discontinuation of the product Neuzym® (lysozyme) by the market authorisation holder (Eisai) in Japan in March 2016 due to the failure of recent post-marketing studies to show statistical significant differences in the efficacy of lysozyme compared to placebo. Based on scientific data available from post-market clinical studies as well as published literature provided by the product registrants, HSA concluded likewise that there was no evidence of efficacy to support the continued clinical use of lysozyme. Despite an established safety profile, the lack of efficacy rendered its use as a therapeutic product unjustifiable.

Regulatory action and HSA's advisory

HSA will be de-registering lysozyme-containing products as therapeutic products in Singapore. Considering the long history of use of lysozyme in Singapore and the acceptable safety profile, the current registration of lysozyme-containing products will continue to be effective until 31 December 2018.

The de-registration of lysozyme-containing products as therapeutic products does not exclude its possibility of them being supplied in the market as other types of health products if they meet the regulatory requirements e.g., health supplements.

EXEMPTIONS FOR SUPPLY OF PRESCRIPTION ONLY MEDICINES

As part of HSA's on-going effort to enhance public access to safe and effective medicines, HSA, in consultation with the Ministry of Health, has allowed a new list of Prescription Only Medicines (POM) to be supplied by pharmacists without prescription with effect from 1 June 2017 (Table 1). In collaboration with the Pharmaceutical Society of Singapore (PSS), HSA has published the Patient Information Leaflets (PIL) for each of these medicines as dispensing aids for pharmacists. These PILs can be found on the 'Reclassified Medicines' webpage on HSA website (refer to the URL links below).

Table 1: Exemption conditions for the sale and supply of POM without prescription (with effect from 1 June 2017)

	Ketotifen oral solid preparations not exceeding 2 mg	Ketotifen oral liquid preparations not exceeding 1 mg / 5 ml	Alcaftadine eyedrops not exceeding 0.25%	Emedastine eyedrops not exceeding 0.05%	Fexofenadine oral liquid preparations not exceeding 6 mg/mL	Fluticasone Furoate Intranasal spray not exceeding 27.5mcg/spray
Indication	Symptomatic treatment of allergic rhinitis and chronic urticaria	Symptomatic treatment of allergic rhinitis and chronic urticaria	Prevention of itching associated with allergic conjunctivitis	Short-term treatment of signs and symptoms of allergic conjunctivitis	For the symptomatic treatment of allergic rhinitis and chronic idiopathic urticaria	Prevention and treatment of allergic rhinitis
Maximum daily dose	2 mg	2 mg	One drop into affected eye once daily	One drop into the affected eye twice daily	60 mg	110 mcg
Maximum supply	10 days	120 mL	3 mL	5 mL	150 mL	3 months
Minimum age	3 years	3 years	3 years	3 years	2 years	18 years

	Triamcinolone topical paste/lotion containing not more than 0.1 % *
Indication	For the treatment of mouth ulcers

* Triamcinolone lotion containing not more than 0.1% can be supplied without a doctor's prescription, in addition to the current exempted triamcinolone paste.

Reclassified Medicines webpage URL:

http://www.hsa.gov.sg/content/hsa/en/Health_Products_Regulation/Western_Medicines/Reclassified_Medicines.html

List of PILs for POM with exemptions for supply without prescription URL:

http://www.hsa.gov.sg/content/hsa/en/Health_Products_Regulation/Western_Medicines/Reclassified_Medicines/Patient_Information_Leaflets.html

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