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HSA Health Sciences Authority

ADVERSE DRUG REACTION NEWS

Contents

GADOLINIUM-BASED CONTRAST AGENTS AND RISK OF GADOLINIUM BRAIN DEPOSITS

Key Points

- There has been increasing scientific evidence suggesting that gadolinium accumulates in brain tissues following multiple administrations of gadolinium-based contrast agents (GBCA)
- Linear agents have a tendency towards higher gadolinium deposition when compared to macrocyclic agents
- No adverse clinical consequences have been identified from gadolinium brain deposition and the long-term clinical significance of gadolinium deposition is presently unknown
- Healthcare professionals are advised to consider the retention characteristics of each GBCA when choosing GBCAs for their patients. They should also use the lowest effective dose of GBCA whenever possible and repeated doses of GBCAs should be administered only after careful benefit-risk assessment

HSA has recently completed its benefit-risk assessment on the potential risk of gadolinium deposition in the brain following repeated administration of GBCAs. This assessment was triggered by recent findings from scientific publications suggesting that gadolinium is retained in the brain after use of GBCAs in magnetic resonance imaging (MRI) scans, as well as the European Medicines Agency's (EMA) decision to suspend the marketing authorisations of selected intravenous (IV) linear GBCAs and restrict the use of another IV linear GBCA in July 2017.[1] HSA's review concluded that while there is currently no definite evidence of clinical harm of gadolinium brain deposition following GBCA administration, healthcare professionals are advised to use the lowest effective dose of GBCA whenever possible as a precautionary measure.

About GBCAs

GBCAs are used to enhance the quality of magnetic resonance (MR) images to improve the diagnostic accuracy of the MRI. GBCAs may be categorised according to their chemical structures, i.e. linear or macrocyclic. Scientific evidence suggests that when compared to macrocyclic agents, the linear agents are more susceptible to dissociation of the chelate and subsequent deposition of free gadolinium in the brain.[2-5] There are six GBCAs registered in Singapore (Table 1) and all of them are indicated for the enhancement of MRI scans of several anatomical structures (e.g. cranial and spinal regions and liver), with the exception of Primovist (gadoxetate disodium), which is approved only for liver MRI scans.

Table 1. Registered GBCAs in Singapore

Brand Name	Active Ingredient	Company	Type
Dotarem	Gadoteric acid	Kenda (S) Pte Ltd	Macrocyclic
Gadovist	Gadobutrol	Bayer (South East Asia) Pte Ltd	Macrocyclic
Primovist	Gadoxetate disodium	Bayer (South East Asia) Pte Ltd	Linear
Multihance	Gadobenate dimeglumine	DCH Auriga Singapore	Linear
Magnevist	Gadopentetate dimeglumine	Bayer (South East Asia) Pte Ltd	Linear
Omniscan	Gadodiamide	GE Healthcare Pte Ltd	Linear

Literature findings

Initial brain imaging studies documented hyperintensities in brain MRI scans of patients who had received multiple GBCAs administrations, leading to the hypothesis that gadolinium is deposited in the brain after repeated GBCA use.[6] This hypothesis was confirmed by post-mortem studies documenting the presence of gadolinium in harvested brain tissues of deceased individuals who had been exposed to repeated GBCAs during their lifetime.[7-8] In addition, the evidence for gadolinium deposition had been found to be much stronger with the less stable linear GBCAs as compared to the macrocyclic agents, suggesting that the propensity of a GBCA

to cause brain deposition could be related to the chemical structure and stability of the GBCA chelate.[3-5] Based on the current available scientific evidence, the presence of gadolinium brain deposits has not been shown to result in clinical adverse effects and the long-term effects are still being studied.

International regulatory actions

International regulatory health authorities, namely the EMA, United States Food and Drug Administration (US FDA), Health Canada, Australia Therapeutic Goods Administration (TGA) and New Zealand Medsafe had conducted safety reviews on the potential risk of gadolinium brain deposition following administration of GBCAs. While all the reviews of these agencies concluded that there was no clinical harm that could be directly attributed to gadolinium brain deposition, EMA recommended the suspension of the marketing authorisations of three IV linear GBCAs (gadopentetic acid, gadodiamide and gadoversetamide) while restricting the use of the IV formulation of the linear agent gadobenic acid to liver scans only as a precautionary measure.[1] No additional restrictions were instituted for macrocyclic GBCAs but EMA advised that they should be used at the lowest doses that enhanced images sufficiently and only when unenhanced body scans were not suitable. The other agencies did not suspend the use of linear GBCAs but strengthened the package inserts (PIs) of the approved GBCAs (both linear and macrocyclic) in their jurisdictions to include information on this potential risk.[9-12]

HSA's benefit-risk assessment and advisory

HSA's assessment took into consideration findings from scientific literature, information provided by the drug companies, local usage of GBCAs, expert opinions of the local radiologists, and actions taken by the international regulatory health authorities. An advisory issued by the College of Radiologists Singapore in 2017 had shared that there was no definitive evidence of Parkinson's disease or other neurological diseases linked to GBCAs. It also stated that GBCAs had a long history of use with clear benefits to patients without major long-term side effects.[13]

HSA has assessed that linear GBCAs still have a place in local clinical practice, particularly in specialised MRIs such as liver and cardiac imaging. Scientific evidence has shown that gadolinium accumulates in brain tissues following multiple GBCA administrations, with a tendency towards higher gadolinium deposition with the linear agents as compared to macrocyclic agents. However, no adverse clinical consequences have been identified and the long-term clinical significance of gadolinium deposition is presently unknown.

To date, HSA has not received any reports of adverse events arising from the accumulation of gadolinium in brain tissues. A Dear Healthcare Professional Letter was issued in March 2018 to enhance healthcare professionals' awareness to this safety issue.[14] HSA is working with the companies to strengthen the local PIs of GBCAs to warn of the potential risk of gadolinium brain deposits.

While the benefit-risk profile of linear GBCAs remains favourable, HSA would like to advise healthcare professionals, in particular radiologists, of the following as a precautionary measure:

- Consider the retention characteristics of each GBCA when choosing GBCAs for patients
- Use the lowest effective dose of GBCA whenever possible and repeated doses of GBCAs should be administered only after careful benefit-risk assessment
- Closely monitor patients who have been administered GBCAs and to report any serious adverse events suspected to be associated with GBCA use

HSA will continue to monitor the international and local developments regarding this safety issue and update healthcare professionals of any new significant findings. Healthcare professionals are encouraged to report any serious adverse events suspected to be related to GBCAs to the Vigilance and Compliance Branch.

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AE CASE IN FOCUS: TEST YOURSELF

Clinical case

A female patient in her 70s with a history of type 2 diabetes mellitus (T2DM) and hypertension was initiated with empagliflozin to improve her glycaemic control. It was added on to her current anti-diabetic medication therapy which included gliclazide, metformin and sitagliptin. She was also taking medications such as hydrochlorthiazide, losartan and nifedipine for her hypertension.

Approximately seven months after starting empagliflozin, she experienced redness and burning in the urogenital area, burning sensation during urination and severe vulvovaginal itching. On consultation with her physician, she was diagnosed with genital infection and urinary tract infection and was treated with antifungal vaginal pessaries and cream.

Question: What could have caused urinary tract infections and genital infections in this patient?

HSA would like to take this opportunity to thank Dr Goh Su Yen, Head of Endocrinology Department at Singapore General Hospital for her professional inputs. Answers can be found on page 6.

RISK OF SEVERE CUTANEOUS ADVERSE REACTIONS WITH RECOMBINANT HUMAN ERYTHROPOIETINS

Key Points

- Overseas cases of severe cutaneous adverse reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported in patients treated with recombinant human erythropoietins (r-HuEPOs)
- These reactions have been more severe with long-acting r-HuEPOs (darbepoetin alfa and methoxy polyethylene glycol-epoetin beta)
- Healthcare professionals are advised to educate their patients on early recognition of allergic reactions, the importance of prompt withdrawal of r-HuEPOs when signs and symptoms suggestive of SCAR appear and the need to seek medical advice

Severe cutaneous adverse reactions (SCAR), including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported overseas in patients treated with r-HuEPOs. Some of these cases were life-threatening or fatal.

Background

r-HuEPOs are a class of biologics generally used for the treatment of anaemia associated with chronic renal failure. Some r-HuEPOs are also indicated for the treatment of anaemia in patients with non-myeloid malignancies receiving chemotherapy, facilitation of autologous blood collection and augmentation of erythropoiesis in the perisurgical period. SCAR occur rarely with r-HuEPOs and more severe reactions have been observed with long-acting r-HuEPOs (darbepoetin alfa and methoxy polyethylene glycol-epoetin beta). Signs and symptoms of SCAR include reddish target-like macules or circular patches often with central blisters on the trunk, skin peeling, ulcers of mouth, throat, nose, genitals and eyes, and can be preceded by fever and flu-like symptoms.

There are four r-HuEPOs registered in Singapore since 1995, namely epoetin alfa (Eprex®, Johnson & Johnson Pte Ltd), darbepoetin alfa (Nesp®, Kyowa Hakko Kirin (Singapore) Pte Ltd), epoetin beta (Recormon®, Roche Singapore Pte Ltd) and methoxy polyethylene glycol-epoetin beta (Mircera®, Roche Singapore Pte Ltd).

International regulatory actions

a) European Medicines Agency (EMA)[1,2]

In July 2017, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) completed its review on SCAR associated with r-HuEPOs. The review was triggered by a new emerging signal of SCAR (in particular SJS and TEN) arising from post-marketing reports. The review assessed all cases worldwide received up to February 2017, and identified a total of 23 reports of SJS and 14 reports of TEN with r-HuEPOs. Of these, a causal association was found for eight reports of SJS and one case of TEN. The more severe reactions were reported with long-acting r-HuEPOs (darbepoetin alfa and methoxy polyethylene glycol-epoetin beta) and included cases with positive dechallenge and positive rechallenge. EMA's analysis of all SCAR cases from their adverse drug reaction (ADR) database (Eudravigilance) and data from companies concluded that SCAR can be considered a very rare class effect of all r-HuEPOs.

Based on its review outcomes, the PRAC recommended that the package inserts (PIs) and patient information leaflets of these products should be strengthened to warn about SCAR and a Dear Healthcare Professional Letter (DHCPL) be issued to communicate this safety issue.

b) Health Canada (HC)[3]

HC also highlighted this safety concern earlier in May 2017, but its review focused mainly on SCAR associated with Aranesp® (darbepoetin alfa). As of 5 April 2017, HC identified 11 cases of SJS and four cases of TEN from international reports of patients treated with darbepoetin alfa across a cumulative exposure of over six million patient-years in the post-marketing setting. The Canadian PI for Aranesp® was updated to include safety information on SCAR.

Local situation and HSA's advisory

To date, HSA has not received any local ADR report of SCAR, SJS or TEN associated with the use of epoetin alfa, darbepoetin alfa, epoetin beta and methoxy polyethylene glycol-epoetin beta. The Singapore PIs for these r-HuEPOs are in the process of being updated to include the risk of SCAR, including SJS and TEN.

Healthcare professionals are advised to educate their patients on the early recognition of signs and symptoms of allergic reactions, the importance of prompt withdrawal of r-HuEPOs when signs and symptoms suggestive of SCAR appear and the need to seek medical advice. They are also encouraged to report suspected ADRs associated with r-HuEPOs including information on the brand name and batch number, to the Vigilance and Compliance Branch of HSA.

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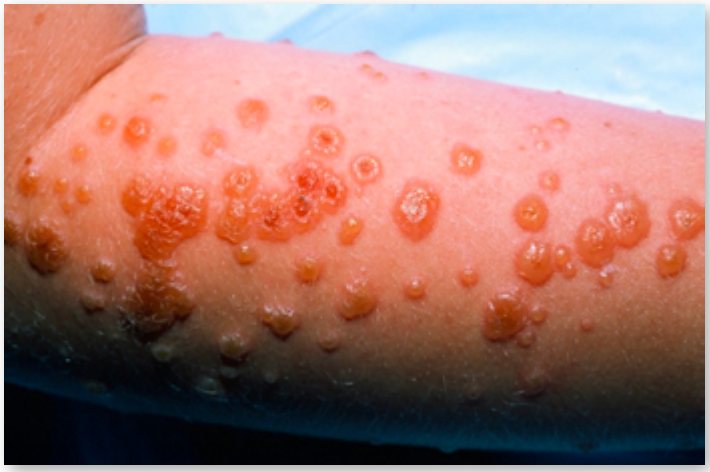


UPDATE ON CANAGLIFLOZIN AND RISK OF LOWER LIMB AMPUTATION

Key Points

- In type 2 diabetes mellitus (T2DM) patients with established cardiovascular (CV) disease or have two or more risk factors for CV events, an approximately two-fold increased risk of lower limb amputation (LLA) was observed in patients treated with canagliflozin compared to placebo
- Regardless of treatment with canagliflozin or placebo, the risk of amputation was highest in patients with a baseline history of prior amputation, peripheral vascular disease and neuropathy
- Healthcare professionals are advised to monitor canagliflozin-treated patients for complications which may precede LLA (e.g. lower-extremity skin ulcer, infection, osteomyelitis, gangrene), and to consider counselling their patients about the importance of routine preventive foot care and maintaining adequate hydration

Canagliflozin (Invokana™, Johnson & Johnson Pte Ltd) is a member of a new class of antidiabetic agents known as sodium-glucose cotransporter-2 (SGLT2) inhibitors. It has been registered locally since February 2014 and is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus (T2DM).

In May 2016, a Dear Healthcare Professional Letter (DHCPL) was issued by the company to inform healthcare professionals about an increased risk of lower limb amputation (LLA) with canagliflozin observed in an ongoing long-term cardiovascular outcome trial (CVOT), called the Canagliflozin Cardiovascular Assessment Study (CANVAS).[1] This article provides an update on the LLA-related safety findings from the integrated analysis of the completed trial and its sister study, as well as the international regulatory actions taken.

CANVAS program and LLA-related safety findings

The CANVAS program comprised two sister studies, CANVAS and CANVAS-Renal (CANVAS-R), which were similar in study design and subject eligibility criteria. The primary objective of the CANVAS study was to evaluate the cardiovascular (CV) risk of canagliflozin while the primary objective of the CANVAS-R study was to assess the effect of canagliflozin on the progression of albuminuria and diabetic nephropathy. The subject population enrolled in both studies was T2DM patients who had inadequate glycaemic control (HbA1c ≥7.0% and ≤10.5%) with either known CV disease or two or more risk factors for CV events. A total of 10,134 subjects were enrolled in these two studies, of which 65% had pre-existing CV disease. Subjects in CANVAS and CANVAS-R studies were followed for an average of 5.7 and 2.1 years, respectively.

Integrated analysis of these two studies was prespecified and aimed to assess the CV safety of canagliflozin, in fulfilment of the US Food and Drug Administration's (FDA) post-marketing requirement.[2] The CANVAS and CANVAS-R studies were initiated in December 2009 and January 2014, respectively, and both studies were completed in February 2017.

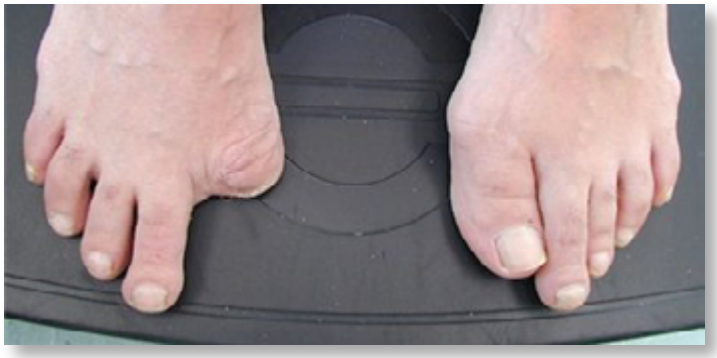
Patients treated with canagliflozin had a lower risk of CV events than those who received placebo. However, an approximately two-fold increased risk of LLA (primarily of the toe and midfoot) was observed in patients treated with canagliflozin compared to placebo (Table 1). The imbalance in LLA incidence occurred as early as the first 26 weeks of therapy, and in a dose-independent manner.

Multiple amputations (some involving both lower limbs) were observed infrequently and in similar proportions in both treatment groups. Regardless of treatment with canagliflozin or placebo, the risk of amputation was highest in patients with a baseline history of prior amputation, peripheral vascular disease and neuropathy. Lower limb infections, diabetic foot ulcers, peripheral arterial disease and gangrene were the most common medical events associated with the need for an amputation in both treatment groups.

Table 1. Integrated analysis of amputation in the CANVAS program

	Placebo (n=4,344)	Canagliflozin (n=5,790)
Total number of subjects with events, n (%)	47 (1.1%)	140 (2.4%)
Incidence rate (per 100 subject-years) [a]	0.34	0.63
Hazard ratio (95% confidence interval) versus placebo	-	1.97 (1.41, 2.75)
Minor amputation, n (%) [b]	34/47 (72.3%)	99/140 (70.7%)
Major amputation, n (%) [c]	13/47 (27.7%)	41/140 (29.3%)

[a] Incidence was based on the number of patients with at least one amputation, and not the total number of amputation events. Some patients had more than one amputation
[b] Toe and midfoot
[c] Ankle, below knee and above knee



Risk of LLA with other SGLT2 inhibitors

To date, the evidence suggesting an increased risk of LLA with SGLT2 inhibitors other than canagliflozin is limited. The CVOT for empagliflozin, known as the EMPA-REG OUTCOME study, did not systematically capture the amputation events. A total of 7,020 T2DM patients with high CV risk, 99.5% of which had pre-existing CV disease, were enrolled in this study.[3] Post-hoc analysis of LLA-related adverse events identified in this study found no difference in the risk of LLA between empagliflozin and placebo (HR 1.00 [95% CI 0.70, 1.44]).[4]

The CVOT of dapagliflozin, known as DECLARE-TIMI 58, is ongoing and expected to be completed in July 2018.[5]

International regulatory actions

(a) European Medicines Agency (EMA)

In April 2016, EMA initiated a safety review to evaluate the risk of

LLA associated with canagliflozin, which was subsequently extended to the other SGLT2 inhibitors (i.e. dapagliflozin and empagliflozin). The safety review, completed in February 2017, concluded that canagliflozin might contribute to the risk of LLA although the mechanism of canagliflozin-induced LLA remained unclear. In addition, although the available data suggesting a class effect of SGLT2 inhibitors on LLA risk were limited, this risk might also apply to other SGLT2 inhibitors.[6] As a result, the European package inserts (PIs) for all SGLT2 inhibitor-containing products were updated to warn about this risk. In contrast to the European PI for canagliflozin which carried specific warnings on canagliflozin and LLA, the updated LLA-related safety information in the European PIs of dapagliflozin- and empagliflozin-containing products provided a more general warning, highlighting the increased risk of LLA with another SGLT2 inhibitor and the unknown class effect of SGLT2 inhibitors on the risk of LLA.[7]

(b) US FDA

The US FDA also conducted a review on this safety issue and issued a safety communication in May 2017, highlighting its recommendation to strengthen the US PIs of canagliflozin-containing products with new warnings, including a boxed warning, on the increased risk of leg and foot amputations.[8]

Local situation and HSA's advisory

To date, HSA has not received any local reports of LLA associated with canagliflozin or other SGLT2 inhibitors. Following the issuance of the DHCPL in May 2016, the local PI for Invokana™ was updated to warn about the risk of LLA, and is currently in the process of being updated to include findings from the integrated analysis of the CANVAS program.

Healthcare professionals are advised to take into consideration the above safety information when prescribing canagliflozin, and to monitor canagliflozin-treated patients for complications which may precede LLA, such as lower-extremity skin ulcer, infection, osteomyelitis or gangrene. They should also consider counselling their patients about the importance of routine preventive foot care and maintaining adequate hydration.

HSA will continue to closely monitor the local and international developments regarding the risk of LLA with SGLT2 inhibitors and will update healthcare professionals of any new significant findings. Healthcare professionals are encouraged to report any serious adverse reactions, including amputations, related to SGLT2 inhibitors to the Vigilance and Compliance Branch of HSA.

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CAUTION ON THE USE OF LYSOZYME-CONTAINING PRODUCTS IN PATIENTS WITH KNOWN EGG ALLERGY

Key Points

- Lysozyme-containing products are derived from eggs and may pose a potential hazard to patients with known egg allergy
- Healthcare professionals are advised to take into consideration egg allergies when prescribing lysozyme-containing products

HSA would like to inform healthcare professionals that lysozyme that is present in lysozyme-containing therapeutic products is derived from egg white, and hence these products have the potential to cause allergic reactions in patients with egg allergies. HSA has recently received an adverse drug reaction (ADR) report of severe cough, urticaria and eczema flare in a child with known egg allergy who was given lysozyme. To date, other ADRs reported with lysozyme-containing products were mainly eye swelling and rashes. HSA will be working with the companies' marketing lysozyme-containing products to update the respective product information labels on this safety information.

About lysozyme-containing products

Lysozyme was first approved in 1989 as an expectorant and mucolytic for chronic sinusitis and treatment for bleeding. A re-evaluation was subsequently conducted following newer scientific data from post-market clinical studies which reported no statistical significant differences in the efficacy of lysozyme compared to placebo. Lysozyme-containing products, (Neuzym® (Eisai (Singapore) Pte Ltd), Leftose (Wellchem Pharmaceuticals Pte Ltd), Neuflo (Yung Shin Pharmaceutical (Singapore) Pte Ltd) and Lyzyme (Zyfas Medical Co), will be phased out as therapeutic products in Singapore by 31st December 2018.[1]

HSA's advisory

Healthcare professionals are advised to check with their patients for any history of egg allergy before prescribing or dispensing lysozyme-containing products to their patients. They are also encouraged to report any suspected serious ADRs related to these products to the Vigilance and Compliance Branch of HSA.

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

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ANSWERS TO AE CASE IN FOCUS: TEST YOURSELF

Genitourinary infections and diabetes

Patients with diabetes are at an increased risk of genitourinary infections. Genitourinary infections include bacteriuria associated with glycosuria, urinary tract infections (UTI) and non-sexually transmitted genital infections, which are usually fungal in nature and present as mycotic vulvovaginitis in women or mycotic balanitis in men.

Based on a UK observational study of type 2 diabetes mellitus (T2DM) patients in primary care, the one-year incidence of UTI among patients (n = 135,920) is about 50% to 60% higher compared to non-diabetic patients (46.9 vs 29.9 per 1000 person-years).[1] The study also showed that patients with T2DM have an increased risk of developing genital infections with the relative risk of 1.81 [1.64-2.00] (RR [95% CI]) for the vaginitis female group and 2.85 [2.39-3.38] for the balanitis male cohort.[1]

Other than the underlying diabetes condition, the study identified other possible risk factors for UTI such as the female gender, pregnancy, older age, history of UTIs in the last six months and poor glycaemic control [glycosylated haemoglobin (HbA1c) > 8.0%].[1] While the risk of developing UTI increases with age, the finding is contrary for genital infection. Studies have shown that the incidence of genital infection is higher among younger adults compared to older adults.[2]

Risk of genitourinary infections with use of SGLT2 inhibitors

While the underlying diabetic condition predisposes T2DM patients to genitourinary infections, the use of SGLT2 inhibitors adds on to this risk. The incidence of UTI reported in clinical trials varies between 4% – 9% for T2DM patients who used SGLT2 inhibitors, with a difference of 1.0 – 1.5% above that reported with placebo. These infections have also been found to be more common in women than in men. Genital infections have been reported to be significantly more common with the use of SGLT2 inhibitors compared to placebo[3-5] and are five times more likely than with other anti-diabetic agents.[2] It is estimated that genital infections affect 5 – 10% of patients using SGLT2 inhibitors and this risk increases in premenopausal women, patients with history of genitourinary infections, and patients who are obese.[6] Most first events of genital infections occurred early in the course of treatment (within six months) and recurrent infections were uncommon.[1] Majority of the infections were treated with standard antifungal therapy (oral and/or topical) while the patients continued their SGLT2 inhibitors. Symptoms usually resolved within a week upon treatment initiation.[2]

The mechanism of action of SGLT2 inhibitors to pharmacologically induce renal glycosuria plays a large role in increasing the risk of genitourinary infections in T2DM patients. The increased urinary glucose concentration creates a favourable environment in the urogenital area for the growth of microorganisms e.g., bacteria and yeast.

In our AE case in focus, while the patient was on empagliflozin, she developed genitourinary infection and was treated with antifungal medication. Despite antifungal treatment, her infection persisted for two months. She discontinued empagliflozin on her own. Her non-compliance with empagliflozin resulted in her mean HbA1c level to increase from 7.6% to 8.3%. When she was switched to another anti-diabetic agent, her HbA1c decreased to 7.7%.

Local reports

As of October 2017, HSA has received 12 reports of genitourinary infection associated with the use of SGLT2 inhibitors. Out of these, six were females and five were males. One report did not list the gender of the patient. Their ages ranged from 49 to 77 years old. Seven reports which had listed UTI (without genital co-infection) affected the older group of patients (63 to 77 years old). This is consistent with the findings from studies that UTI generally affects older adults as compared those at risk of genital infections. The five patients who had experienced genital infection were aged between 49 to 68 years old. One of the report did not indicate the patient's age and the other reported both genital and urinary infection (cystitis). One patient was noted to be clinically overweight (83kg, 27.7kg/m^2) and another was clinically obese class III (107kg, 43.4kg/m^2) [weight, Body Mass Index (BMI)]. Of the 12 cases, six patients had developed the infection within two months after initiating SGLT2 inhibitor treatment. Latency was not reported in four of the cases while only two patients developed the infection after seven months.

Please refer to Table 1 for the number of AE reports of genitourinary infections submitted to HSA by public healthcare institutions and the drug utilisation rates of different SGLT2 inhibitors.

Potential for non-compliance and/or discontinuation

Although genitourinary infections are generally deemed as non-serious, the severity of the symptoms experienced (pruritus, soreness, redness in the genital area) may be discomforting and unbearable, resulting in patients being non-compliant with their SGLT2 inhibitors therapy.

In three of the local cases, it was reported that patients' adherence to SGLT2 inhibitors therapy were compromised due to the intolerable symptoms of genitourinary infections, resulting in deterioration in their glycaemic control. One of the patient's HbA1c levels increased to 8.7% during the infection period.

International individual case safety reports (ICSRs) from the World Health Organisation's (WHO) global safety database (VigiBase) revealed similar occurrences where patients stopped taking these medications because of the genital infection adverse events (AE).[6]

Most genital infections reported in clinical trials were mild to moderate and only rarely led to discontinuation of treatment.[3-5] However, such 'non-serious' AEs may manifest in the post marketing period as severe events which may have large enough impact on the patient's quality of life that discontinuation of the medication is deemed necessary.[6]

HSA's advisory

HSA encourages healthcare professionals to closely monitor patients on SGLT2 inhibitors and be vigilant to seemingly non-serious AEs such as genitourinary infections which in severe cases could potentially adversely affect patients' quality of life and compliance of their SGLT2 inhibitor therapy. This may result in poor glycaemic control and potentially lead to serious life-threatening consequences e.g., hyperglycaemia with ketoacidosis. Healthcare professionals are advised to report any

suspected adverse events associated with the use of SGLT2 inhibitors to the Vigilance and Compliance Branch of HSA. Your support of the national safety monitoring programme is invaluable in safeguarding public health.

Table 1. No. of AE reports from the public healthcare institutions (excluding company reports) and the drug utilisation rates with the different SGLT2 inhibitors

SGLT2 inhibitor	No. of genitourinary infection reports	DDD*	Reports/million DDD
Canagliflozin	1	419,370	2.38
Dapagliflozin	3	1,084,636	2.76
Empagliflozin	5	764,430	6.54

**DDD:Defined daily dose for public healthcare institutions & Raffles Hospital; 2014 - Sep 2017 Data source: IMS Health.*
The figures in Table 1 are current up to October 2017. The information above is to provide a crude baseline comparison between the number of reports received with the utilisation of SGLT2 inhibitors. The data provided should not be used to draw comparisons on the safety of different brands of SGLT2 inhibitors as this is confounded by factors such as extent of use, the patient populations exposed and under-reporting. It does not include private hospital reports. It does not represent a risk assessment of this class of drugs.

References

1. *Diabetes Res Clin Pract. 2014:103(3):373-81*
2. *Prescriber 2016:27(12):26-30*
3. *European Medicines Agency. Jardiance (empagliflozin) public assessment report, March 2014*
4. *European Medicines Agency. Forxiga (dapagliflozin) public assessment report, September 2012*
5. *European Medicines Agency. Canagliflozin public assessment report, September 2013*
6. *WHO Pharmaceuticals Newsletter No. 3, 2017:Pg 23-25*

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.

LIST OF DEAR HEALTHCARE PROFESSIONAL LETTERS ON SAFETY CONCERNS ISSUED BY HSA, PHARMACEUTICAL AND MEDICAL DEVICE COMPANIES (1 DEC 2017 TO 30 APRIL 2018)

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

Therapeutic products

11 Dec 2017	**Ofev® (nintedanib)** Safety information regarding incidence of drug-induced liver injury in patients with idiopathic pulmonary fibrosis treated with Ofev®
15 Dec 2017	**Xofigo® (radium-223 dichloride)** Safety information regarding increased incidence of deaths and fractures in patients with Xofigo® used in combination with abiraterone acetate and prednisolone/prednisone
20 Feb 2018	**Esmya® Tablet 5mg (Ulipristal Acetate)** Safety update on the potential risk of liver injury associated with Esmya
5 Mar 2018	**Gadolinium-based contrast agents** Safety update on the potential risk of gadolinium deposition in the brain following repeated use of gadolinium-based contrast agents (GBCA)
13 Mar 2018	**Maxipime® (cefepime)** Reminder on the risk of serious neurologic AEs, including encephalopathy, associated with cefepime particularly in patients with renal impairment
15 Mar 2018	**Epilim® (sodium valproate, valproic acid)** Reminder on the risk of congenital malformations and serious developmental disorders in children who are exposed in utero to Epilim® and precautions to consider when it is used during pregnancy
21 Mar 2018	**Baxter Sodium Chloride Injection 0.9% USP 500 mL solution** Test conducted showed that the PH of the solution was lower than 4.5 after 18 months of storage. However, there was no impact to the quality of the affected product

Medical devices

14 Dec 2017	**MCK TIBIAL BASEPLATE-RM/LL-SZ 2 and MCK TIBIAL BASEPLATE-RM/LL-SZ 7** Voluntary lot-specific recall of affected devices due to the packaging of certain sizes and lots containing the incorrect device and/or label
4 Jan 2018	**SynchroMed® II implantable drug infusion pump** Update on the design change in order to reduce the likelihood of non-recoverable motor stall, which can cause loss of therapy
10 Jan 2018	**Cardiac Resynchronization Therapy pacemakers (VALITUDE™, VISIONIST™) and defibrillators (CHARISMA™ , MOMENTUM™, RESONATE™, VIGILANT™, AUTOGEN™, DYNAGEN™, INOGEN™, ORIGEN™)** Update on the reprogramming of the device to prevent the unintended asynchronous biventricular (BiV) pacing behaviour when tracking elevated atrial intrinsic rhythms in patients
1 Feb 2018	**Pacemakers (ACCOLADE™, PROPONENT™, ESSENTIO™, ALTRUA™) and Cardiac Resynchronization Therapy pacemakers (VALITUDE™, VISIONIST™)** Update on the development of a software to mitigate the occurrence of intermittent oversensing of the Minute Ventilation (MV) sensor signal reported with its use
22 Feb 2018	**Capio™ SLIM Open Access Suture Capturing Device and the Uphold™ LITE with Capio™ SLIM Vaginal Support System** Updates on Capio™ suture management technique and directions of use to prevent excessive counter-traction during deployment of the affected devices
6 Mar 2018	**VertaPlex, VertaPlex HV and SpinePlex Radiopaque Bone Cement products** Labelling updates to the Instructions For Use of the affected devices on the risks of cement leakage into the venous system resulting in embolism of the lung and/or heart or other clinical sequelae
13 Apr 2018	**Segmental System Proximal Femoral Component 38mm Offset** Voluntary lot-specific recall of affected device due to complaint of debris in the hole on the affected device's superior lateral aspect

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS AND CARDIOVASCULAR RISK – AN UPDATE AND REMINDER

Non-steroidal anti-inflammatory drugs (NSAIDs) are known to be associated with a small but increased cardiovascular (CV) risk, such as myocardial infarct (MI) or stroke. There has been increasing evidence that the CV risk may appear within days to weeks of NSAIDs initiation.[1-3] In addition, published scientific literature has reported that the increased CV risk associated with high-dose diclofenac (150mg/day) and high-dose ibuprofen (2,400mg/day) is comparable to that of the COX-2 inhibitors.[4]

In view of the above, HSA would like to remind healthcare professionals about the CV warnings for NSAIDs, including that for high-dose diclofenac and high-dose ibuprofen, as well as highlight some counselling points for NSAIDs.

Cardiovascular warnings

All NSAIDs (excluding low-dose aspirin)

- All NSAIDs should be prescribed at the lowest effective dose and the duration of treatment should be periodically reviewed and kept as short as possible
- Non-selective NSAIDs (e.g. diclofenac, ibuprofen) may be associated with a small increase in the absolute risk of CV events (e.g. MI and stroke), especially when used at high doses for long-term treatment
- All NSAIDs should not be prescribed in patients who have recently undergone coronary artery bypass graft (CABG) surgery and revascularisation procedures

High-dose diclofenac (150mg/day)

- The use of high-dose diclofenac (150mg/day) for more than four weeks is contraindicated in patients with established CV disease (congestive heart failure, established ischaemic heart disease, peripheral arterial disease) or uncontrolled hypertension
- If diclofenac treatment is needed, patients with established CV disease, uncontrolled hypertension or significant CV risk factors (e.g. hypertension, hyperlipidaemia, diabetes mellitus and smoking) should be treated only after careful consideration and at doses ≤100mg daily if the treatment is for more than four weeks

High-dose ibuprofen (2,400mg/day)

- Clinical studies suggest that use of ibuprofen, particularly at a high dose (2,400mg/day), may be associated with a small increased risk of arterial thrombotic events (e.g. MI or stroke)
- Overall, epidemiological studies do not suggest that low-dose ibuprofen (≤1,200mg/day) is associated with an increased risk of arterial thrombotic events, particularly MI
- Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration and high doses (2,400mg/day) should be avoided
- Careful consideration should also be exercised before initiating long-term treatment in patients with risk factors for CV events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking), particularly if high doses of ibuprofen are required

Counselling points for NSAIDs (excluding low-dose aspirin)

Healthcare professionals may wish to consider the following counselling points for patients who are taking NSAIDs:

- NSAIDs (excluding low-dose aspirin) may be associated with a small increased risk of heart attack or stroke. Any risk is more likely with high doses or prolonged treatment. Do not exceed the recommended dose and duration
- The lowest effective dose should be taken for the shortest possible time to reduce the risk of side effects

HSA's advisory

Healthcare professionals are advised to consider the above CV warnings when prescribing or dispensing NSAIDs to their patients.

References

1. *Eur Heart J 2006; 27: 1657-63*
2. *Circulation 2011; 123: 2226-35*
3. *Clin Pharmacol Ther 2009; 85:190-7*
4. *Lancet 2013; 382: 769-79*

Please send your enquiries, comments and suggestions to:

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