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RISK OF SERIOUS LIVER INJURY WITH ESMYA (ULIPRISTAL ACETATE)

Key Points

- ❖ Overseas cases of serious liver injury, including four cases which required liver transplantation, have been reported in women treated with Esmya®
- ❖ The mechanism by which Esmya® may potentially cause liver injury remains uncertain, and no pattern in the timing between Esmya® treatment and the occurrence of liver injury has been identified
- ❖ Healthcare professionals are advised to monitor the liver function of their patients before, during and after treatment with Esmya®



HSA would like to bring to the attention of healthcare professionals the risk of serious liver injury associated with the use of Esmya® (ulipristal acetate 5 mg). Overseas cases of serious liver injury have been reported in women who had received treatment with Esmya®, including four cases which required liver transplantation. At this time, this safety concern has not been observed with another registered product containing the same active ingredient (Ella®, ulipristal acetate 30 mg) used for emergency contraception.

Background

Esmya® (Zuellig Pharma Pte Ltd) is an oral selective progesterone receptor modulator (SPRM) that has been registered in Singapore since November 2014. It is indicated for pre-operative treatment, as well as intermittent treatment, of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. The treatment consists of 5mg once daily for treatment courses of up to three months each. Esmya® exerts a direct action on fibroids, reducing their size through inhibition of cell proliferation and induction of apoptosis. Esmya® also has a direct effect on the endometrium, which contributes to the reduction in uterine bleeding.

Overseas post-marketing cases of liver injury with Esmya¹

Esmya® was first authorised in the European Union in February 2012. As of February 2018, the post-marketing exposure to Esmya® was estimated at approximately 200,000 to 275,000 patient-years, assuming a mean treatment duration of three months. From February 2012 to February 2018, 105 post-marketing cases of hepatic disorders have been reported overseas with the use of Esmya®, of which 34 cases were assessed to be serious. Esmya® was considered as a potential contributing factor for causing liver injury in eight of the serious cases, including four cases of acute liver failure leading to liver transplantation. A contributing role of Esmya® in the development of acute liver failure in two of the cases was assessed to be probable, while insufficient information was available to either conclude or rule out a causal relationship with Esmya® for the remaining two cases.

For the other four serious cases of liver injury, although a causal role of Esmya® was considered possible, available information was insufficient to draw firm conclusions on causality. The possible causal associations for these cases were mainly supported by positive de-challenge, absence of other confounding factors, or explanations for the observed liver injury.

At this time, the mechanism by which Esmya® could potentially cause liver injury remains uncertain, and no clear pattern in the timing between Esmya® treatment and the occurrence of liver injury has been identified. Based on the reported post-marketing cases of potential liver injury with Esmya®, regardless of causality, the peak time-to-onset of liver injury is approximately 140 days, with the majority of the reported potential drug-induced liver injuries occurring within one and eight months of starting treatment with Esmya® (i.e. two treatment cycles, including two months of treatment-free interval).

International regulatory actions²⁻⁴

The European Medicines Agency (EMA), New Zealand Medsafe and Health Canada have conducted safety reviews on this risk, following reports of serious liver injury leading to liver transplantation after treatment with Esmya®. Their reviews took into consideration the available data from non-clinical and clinical



AE CASE IN FOCUS: TEST YOURSELF

A 78-year-old man presented to the emergency room with acute kidney injury after a recent percutaneous coronary angioplasty for non-ST elevation myocardial infarction, on a background of chronic renal impairment. This was complicated by hyperkalaemia of serum potassium level of 6.8 mmol/L without ECG changes. He denied having chest pain, acute shortness of breath, headache or dizziness. His physical examination was unremarkable and the laboratory investigations revealed raised creatinine at 276 umol/L from a baseline of 130 to 150 umol/L.

He was administered insulin/dextrose and an intravenous (IV) calcium gluconate infusion of 10 % diluted in 100 ml of normal saline over 30 minutes via a peripheral cannula set on the left hand dorsum. Subsequently, his entire left forearm and hand were noted to be cool and cyanosed with absence of pulse. He was referred for vascular opinion on the possibility of acute limb ischemia. On assessment, there was monophasic signal on Doppler ultrasound over the radial artery, with two small (2 cm) blood blisters at the IV access and another attempted site on the forearm. There was mild weakness with power of 4/5, and he complained of coldness of the forearm and hand (no pain or numbness). A therapeutic dose of subcutaneous enoxaparin was administered, and all signs and symptoms resolved after two hours.

The following day, a duplex arterial ultrasound assessment of the left upper limb (Figure 1 on page 8) revealed a focal chronic occlusion of the left proximal subclavian artery with retrograde flow in the left vertebral artery, without any significant lesions in the rest of the arm. His finger pressures measured at 94 mmHg on the ipsilateral* and 115 mmHg on the contralateral* sides with monophasic radial and ulnar signal in the affected hand. There was also a reduced systolic blood pressure in the affected arm (126 mmHg on the left and 159 mmHg on the right). These findings were consistent with a diagnosis of chronic subclavian steal syndrome (SSS).

About subclavian steal syndrome (SSS)

Subclavian steal syndrome occurs when there is either a high grade stenosis or total occlusion of the subclavian artery proximal to the origin of the vertebral artery, resulting in retrograde flow in the ipsilateral vertebral artery (Figure 2 on page 8). The prevalence is low at 0.6 - 6.4% of the population.^{1,2} Most patients (95 %) are asymptomatic,³ and the phenomenon is often an incidental finding as there is an abundance of collateral blood supply from the head, neck and shoulder supplied via flow reversal in the vertebral artery. The symptoms usually relate to inadequate collateral circulation with inadequate perfusion of the vertebrobasilar system (presenting as paroxysmal vertigo or syncopal attacks, dizziness, diplopia, ataxia or dysarthria) or ischemia to the hand (manifesting as arm pain, weakness, numbness, coldness or claudication).

SSS has a left-sided preponderance of 82 %, ⁴ as was the case in this patient. Existing literature pertaining to a provoked SSS often describe exertion as the precipitant, which increases metabolic demands and causes vasodilation, and thereby manifesting as arm claudication, or symptoms of acute insufficiency.

Question:

Could the patient's symptoms be attributed to the calcium gluconate infusion? What are the possible mechanisms?

Answers can be found on page 8.

HSA would like to thank Dr Tay Hsien Ts'ung from the Department of Vascular and Endovascular Surgery, Singapore General Hospital, and Dr Janice Tan Shih Jia, Department of General Surgery, Sengkang General Hospital, for their contributions to this article.

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studies, spontaneously reported post-marketing data, as well as information from scientific literature. Based on the review of available information, all three agencies had concluded that the use of Esmya[®] (or Fibrisal, the brand marketed in Canada) could have contributed to the development of serious liver injuries, and additional measures should be implemented to mitigate this risk. These included contraindicating the use of Esmya[®] in women with underlying liver disorders, requiring liver function monitoring to be performed before, during and after stopping treatment with Esmya[®], as well as restricting the use of multiple treatment courses of Esmya[®] to women who were not eligible for surgery for treatment of the fibroids.

Local situation and HSA's advisory

As of June 2019, HSA has received two non-serious local adverse event reports of elevations in liver function tests that were assessed to be possibly related to the treatment with Esmya[®]. In both cases, the increase in liver enzymes were less than three times the upper limit of normal, and were observed approximately two weeks or three months after the initiation of treatment with Esmya[®]. Treatment discontinuation was reported in one case, with a subsequent decrease in the patient's liver enzymes approximately one month later.

HSA has reviewed the available information on liver injury associated with Esmya[®] and assessments conducted by other regulatory agencies. We took into consideration our local adverse event reports, expert opinions from local clinicians and the company-initiated amendments to the local Esmya[®] package insert (PI). To mitigate the risk of serious liver injury associated with the use of Esmya[®], the company will be strengthening the local PI of Esmya[®] to contraindicate its use in patients with underlying liver disorders, as well as recommend more stringent criteria for liver function monitoring (i.e. before starting each treatment course, monthly during the first two treatment courses, and two to four weeks after stopping treatment with Esmya[®]). The indications for Esmya[®] will also be revised to clarify its use as a single treatment course when used in the pre-operative setting, and to restrict its use to adult women of reproductive age not eligible for surgery when used for the intermittent treatment of moderate to severe symptoms of uterine fibroids. In addition, Zuellig Pharma has developed a patient information brochure, for distribution to patients through their healthcare professionals, to inform patients about the potential risk and the signs and symptoms of liver injury to look out for during treatment with Esmya[®]. This brochure has been reviewed and approved by HSA.

Healthcare professionals are advised to take into consideration the above safety information when prescribing Esmya[®]. They may wish to consider using the patient information brochure to counsel patients treated with Esmya[®] on the need to monitor for signs and symptoms of liver injury (e.g. yellowing of the skin, fatigue or excessive tiredness, nausea and vomiting) during and after treatment. Healthcare professionals are also encouraged to report to HSA any suspected cases of liver injury related to the use of Esmya[®].

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*Glossary

Ipsilateral	Occurring on the same side of the body. In this case, it refers to the left side, where the subclavian steal syndrome occurred
Contralateral	Occurring on the opposite side of the body
Vertebrobasilar insufficiency	A condition characterised by poor blood flow to the posterior portion of the brain, which is fed by two vertebral arteries that join to become the basilar artery

BIOTIN INTERFERENCE WITH CLINICAL LABORATORY TESTS

Key Points

- ❖ Biotin may interfere with laboratory tests, leading to either falsely decreased or falsely increased test results. This poses a potential risk for delayed or wrong diagnoses and/or unnecessary treatments. For instance, biotin interference could lead to falsely depressed thyroid stimulating hormone (TSH), and falsely elevated free triiodothyronine (T_3) and free thyroxine (T_4), which could result in a misdiagnosis of Graves' disease
- ❖ Healthcare professionals are advised to consider the possibility of biotin interference when ordering laboratory tests for their patients and when interpreting laboratory results (especially if the results do not match the clinical presentation and/or other investigations)
- ❖ This may involve asking their patients about the use of biotin-containing health supplements, including those marketed for hair, skin and nail growth, as biotin in the patients' specimens could result in the generation of incorrect test results

Biotin can significantly interfere with certain clinical laboratory tests, resulting in incorrect laboratory values. Potential biotin interference has been identified with oral products containing ≥ 150 mcg biotin per dose unit and parenteral products containing ≥ 60 mcg biotin per dose unit. If undetected, the incorrect test results might lead to misdiagnosis or inappropriate patient management.

Biotin, also known as vitamin B7, is a water-soluble vitamin that acts as an enzyme cofactor in various metabolic processes. There are three parenteral products containing biotin registered locally, namely Cernevit® (Baxter Healthcare Asia Pte Ltd), Soluvit™ N (Fresenius Kabi Singapore Pte Ltd), and Tamipool® (Medipharm Pte Ltd). All three products are multivitamin infusions containing ≥ 60 mcg biotin per dose unit. They are indicated as a supplement in intravenous nutrition to meet the daily requirements of vitamins, when oral administration is either contraindicated, impossible or insufficient (e.g. due to malnutrition or gastrointestinal malabsorption). Biotin can also be found in health supplements for oral use, such as multivitamins, prenatal vitamins, and products promoting hair, skin and nail growth.

Biotin interference with clinical laboratory tests

Some laboratory tests are based on a streptavidin-biotin interaction to determine a variety of biomarkers, including hormones, cardiac markers, tumour markers, and infection markers, as well as to determine the concentration of drugs. Biotin is not expected to interfere with laboratory tests when taken at levels found naturally in food or at amounts near the recommended daily intake of 30 mcg.¹ However, in patients taking biotin-containing products at higher doses, competition with biotinylated reagents may result in clinically significant false results (i.e. incorrectly increased or decreased) in these tests. This poses a potential risk for delayed diagnosis, wrong diagnoses and unnecessary treatments. For instance, biotin interference could lead to falsely depressed thyroid stimulating hormone (TSH), and falsely elevated free triiodothyronine (T_3) and free thyroxine (T_4), which could result in a misdiagnosis of Graves' disease.

The risk of obtaining incorrect test results due to biotin is higher in patients receiving high-dose biotin therapy for certain conditions (e.g. multiple sclerosis or rare metabolic disorders), renal failure patients, neonates, children and pregnant women. The popularity of dietary supplements marketed for improving hair, skin and nail health has also been reported to contribute towards the increasing use of high-dose biotin.

International regulatory actions

In January 2019, the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) concluded that there was sufficient evidence to support a potential interference with clinical laboratory tests of oral medicinal products containing ≥ 150 mcg biotin per dose unit, and parenteral medicinal products containing ≥ 60 mcg biotin per dose unit.² The EMA PRAC requested for the product information of these products to be updated to reflect this risk.

Apart from the EMA PRAC, the US Food and Drug Administration (US FDA) had issued a safety communication in November 2017 to alert the public, healthcare professionals, laboratory personnel and laboratory test results developers on the potential interference of laboratory tests with the use of biotin.³ The FDA had highlighted an increase in the number of reported adverse events related to this risk, including one death arising from falsely low troponin test results. The agency informed that it would work with stakeholders to better understand the issue, and to develop additional future recommendations for safer testing in patients who had taken high levels of biotin when using laboratory tests that use biotin technology.

Local situation and HSA's advisory

To date, HSA has not received any local adverse event reports of biotin interference causing incorrect laboratory results. The local package inserts of parenteral biotin-containing products are being updated to include warnings on this interference, and a company-initiated Dear Healthcare Professional Letter was also issued for Soluvit™ N in May 2019 to highlight this risk.

Healthcare professionals are advised to consider the possibility of biotin interference when ordering laboratory tests for their patients and when interpreting laboratory results (especially if the results do not match the clinical presentation and/or other investigations). This may involve asking their patients about the use of biotin health supplements, including those marketed for hair, skin and nail growth, as biotin in the patients' specimens could result in the generation of incorrect test results. As a general precaution, some local hospital laboratories have advised patients to stop biotin therapy for at least 12 hours before blood sample collection is done to minimise falsely increased/decreased laboratory results arising from biotin interference.^{4,5}

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RISK OF ACUTE PANCREATITIS AND CONGENITAL MALFORMATIONS ASSOCIATED WITH THE USE OF CARBIMAZOLE OR THIAMAZOLE

Key Points

- Data from overseas case reports and epidemiological studies identified a new risk of acute pancreatitis and further strengthened the evidence of an increased risk of congenital malformations after treatment with carbimazole or thiamazole
- Healthcare professionals should consider immediate discontinuation of carbimazole and thiamazole if acute pancreatitis is suspected. Re-exposure to carbimazole or thiamazole in these patients might result in recurrence of acute pancreatitis with a decreased time-to-onset
- For the risk of congenital malformations, healthcare professionals are encouraged to counsel women of childbearing potential on the importance of using effective and reliable contraception during treatment with carbimazole or thiamazole. When carbimazole or thiamazole is prescribed during pregnancy following a positive benefit versus risk assessment, the lowest effective dose should be used together with close maternal, foetal and neonatal monitoring

HSA would like to bring the attention of healthcare professionals to overseas case reports of acute pancreatitis with the use of carbimazole or thiamazole and to update on the known risk of congenital malformations associated with these products.

Carbimazole and its active metabolite thiamazole (synonym: methimazole) are antithyroid agents that inhibit the activity of thyroid peroxidase, a key enzyme in thyroid hormone biosynthesis. Carbimazole and thiamazole have been registered in Singapore since 1990 and 1997, respectively. They are indicated for the treatment of hyperthyroidism, including preparation for thyroidectomy and treatment before and after radioiodine therapy.

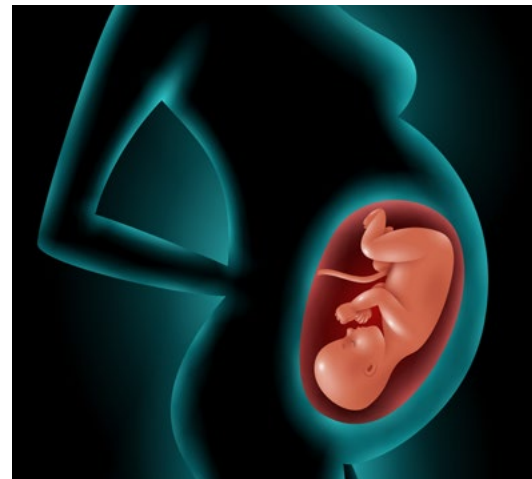
Findings from published case reports and epidemiological studies

a) Risk of acute pancreatitis

Overseas cases of carbimazole- and thiamazole-induced acute pancreatitis have been reported in literature.¹⁻⁸ The majority of these cases involved females and patients aged 55 years and above, who developed acute pancreatitis within two to three weeks following initiation of carbimazole or thiamazole therapy (range: four days to three months). Known risk factors for pancreatitis (e.g. hypertriglyceridemia, chronic alcohol consumption, cholelithiasis, autoimmune diseases) were ruled out by the reporting physician or denied by the patient. Positive dechallenge was seen in all these patients, whose symptoms and examination findings improved following withdrawal of carbimazole or thiamazole and conservative treatment. Re-introduction of carbimazole or thiamazole to some patients led to recurrent acute pancreatitis with a decreased time-to-onset (TTO) (i.e. after the single or second dose of carbimazole or thiamazole in most of the cases), suggesting an immune-mediated mechanism. Although the sulfhydryl group of carbimazole and thiamazole has been postulated to be involved in the drug-induced autoimmunisation,^{1,3} its exact role in the development of acute pancreatitis remains to be confirmed.

b) Update on risk of congenital malformations

Carbimazole and thiamazole are known to cross the placenta and are suspected to cause congenital malformations. Recent studies have provided further evidence of an increased risk of congenital



malformations with carbimazole or thiamazole use during pregnancy. A recent meta-analysis of 12 published case-control and cohort studies demonstrated that exposure to carbimazole or thiamazole during pregnancy increased the risk of congenital malformations compared to no antithyroid drug exposure (odds ratio [OR] 1.88; 95% confidence interval [CI] 1.33-2.65).⁹ In addition, a Korean nationwide cohort study using a prescription claims database observed a 1.3-fold (95% CI 1.06-1.63) increased congenital malformation risk with exposure to thiamazole during the first trimester compared with pregnancies without antithyroid drug prescriptions, corresponding to 17 additional congenital malformation cases (95% CI 1.94-32.15) per 1,000 live births.¹⁰ The authors also found that high cumulative thiamazole dose (> 495 mg) was associated with a 1.87-fold (95% CI 1.06-3.30) increased congenital malformation risk compared with low cumulative dose (up to 126 mg). The mechanism underlying carbimazole or thiamazole embryopathy remains unknown, and the contribution of maternal hyperthyroidism to the risk of congenital malformations is poorly understood.

Regulatory actions taken by EMA

In January 2019, the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) issued its recommendations on the risk of acute pancreatitis and congenital malformations with carbimazole and thiamazole.¹¹ The committee's review of the EudraVigilance (the European adverse event database) and literature identified post-marketing reports of acute pancreatitis with carbimazole or thiamazole. In the cases reporting recurrent acute pancreatitis, a decreased TTO after re-exposure to carbimazole or thiamazole was noted, suggesting a possible immunological mechanism. The committee considered that the available data demonstrated an association between both carbimazole and thiamazole with acute pancreatitis. As a result, the European product information (PI) for carbimazole- and thiamazole-containing products will be updated to include a warning on the risk of acute pancreatitis and a contraindication for use in patients with a history of acute pancreatitis after administration of carbimazole or thiamazole.

The PRAC also concluded that data from case reports and epidemiological studies further strengthened the evidence for an increased risk of congenital malformations with carbimazole and thiamazole use, especially when administered in the first trimester of pregnancy and at high doses (15 mg or more of carbimazole daily).¹² Reported malformations included aplasia cutis congenita (absence of a portion of skin, often localised on the head), craniofacial malformations (choanal atresia; facial dysmorphism), defects of the abdominal wall and gastrointestinal tract (exomphalos, oesophageal atresia, omphalo-mesenteric duct anomaly), and ventricular septal defect. Consequently, the European PIs for carbimazole- and thiamazole-containing products will be updated with new advice on contraception and pregnancy, including use of effective contraception during treatment in women of childbearing potential during treatment, as well as close maternal, foetal and neonatal monitoring when carbimazole or thiamazole is used during pregnancy.

Local situation and HSA's advisory

To date, HSA has received one local report of pancreatitis associated with carbimazole use in a 69-year-old female, with no further details provided. No local reports of congenital malformations associated with carbimazole or thiamazole use have been received. In March 2019, a Dear Healthcare Professional Letter was issued by the product registrant for Thyrozol® (Merck Pte Ltd) to inform healthcare professionals about these safety concerns.¹³ The local package inserts for all carbimazole- and thiamazole-containing products will be updated to warn about these risks, including a new contraindication for use in patients with a history of acute pancreatitis after administration of carbimazole or thiamazole, and a new recommendation to use effective contraception during treatment.

Healthcare professionals are advised to take into consideration the above safety information when prescribing carbimazole and thiamazole. If acute pancreatitis is suspected, healthcare professionals are advised to consider immediate discontinuation of carbimazole and thiamazole. These drugs should also be avoided in patients with a history of acute pancreatitis following administration of carbimazole or thiamazole as re-exposure might result in a recurrence of acute pancreatitis with a decreased TTO.

Healthcare professionals are encouraged to counsel women of childbearing potential on the importance of using effective and reliable contraception during treatment with carbimazole or thiamazole. When carbimazole or thiamazole is prescribed during pregnancy following a positive benefit versus risk assessment, the lowest effective dose should be used together with close maternal, foetal and neonatal monitoring.

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WHAT TO DO IF YOU SUSPECT A PRODUCT DEFECT

HSA has in place a post-market surveillance programme to monitor the quality, safety and efficacy of therapeutic products (TPs) in Singapore. One component of this programme includes product defect management. Product registrants, manufacturers, importers and suppliers of TPs are required by law to report product defects of their registered TPs to HSA to ensure that product defects are promptly investigated, assessed and measures are put in place to safeguard public health.

Product defects can arise during the manufacture, storage and/or handling of the products. As healthcare professionals, you can play a part in ensuring patient safety by reporting product defects to your product suppliers. Some examples of product defects include:

- Product mix-ups e.g. wrong product packed in container or blister
- Microbial contamination
- Physical contamination with foreign materials
- Incorrect information such as dosing, strength or ingredient on the product label, which can lead to serious consequences in patients

To know more about product defects, you may watch the e-video titled 'Requirements and Processes for Product Defect Reporting and Recalls of Therapeutic Products'.

This e-video can be found on the 'Product Defect Reporting and Recall Procedures' webpage on HSA website: https://www.hsa.gov.sg/pdt_defect and on YouTube: <https://youtu.be/3OrHKggrjm4>



Figure 1. E-video published on the 'Product Defect Reporting and Recall Procedures' webpage on HSA's website



Figure 2. E-video published on YouTube

QUIZ TIME!

Try the quiz below to know more on product defects of therapeutic products:

1. All defective products will be recalled from the market.
 - a. True
 - b. False
2. Importers, including hospitals, clinics and retail pharmacies importing an unregistered therapeutic product for patients' use under special access route, must report product defects to HSA.
 - a. True
 - b. False
3. What are the types of risk mitigation measures that can be taken?
 - a. Issuance of Dear Healthcare Professional Letter
 - b. Issuance of Dear Purchaser Letter
 - c. Product recall (removal of a marketed product from market)
 - d. Public announcement through press release
 - e. Product labelling changes
 - f. Manufacturing process improvements to rectify the defect
 - g. Any of the above

Answers can be found on page 7



REGULATORY UPDATE ON BIOSIMILARS

The Health Sciences Authority (HSA) would like to share a statement on the confidence in biosimilar products by international regulators. This is a joint effort under the International Coalition of Medicines Regulatory Authorities (ICMRA) of World Health Organisation (WHO) to support global adoption of biosimilars.

ICMRA/WHO statement about confidence in biosimilar products (for healthcare professionals)

Purpose:

ICMRA/WHO present this statement on biosimilars to provide assurance on the robust regulatory processes for the approval and monitoring of these medicines, and to highlight the benefits they can provide for patients and healthcare systems in terms of increased treatment alternatives, access and cost competitiveness.

ICMRA brings together the heads of 29 medicines regulatory agencies¹ from every region in the world, with the WHO as an observer. Medicines regulators recognise the important role we play in facilitating the provision of access to safe, effective, high-quality products that are essential to human health and well-being. This includes advancing the biology needed to set standards and inform decision-making, as well as maintaining efficient regulatory processes that support the development and delivery of innovative medicinal products while ensuring the benefits of these products outweigh the risks.

Statement:

Biosimilars¹ are biological medicines of proven pharmaceutical quality. Biosimilars are manufactured to the same stringent regulatory standards as other biological medicines. Comprehensive pharmaceutical quality information (chemistry, manufacturing and control) is required.

Biosimilars are approved after rigorous scientific evaluation by regulatory authorities. The concept of biosimilar development and approval is different from originator biologicals, in that the purpose is to demonstrate that the biosimilar is highly similar to the originator medicine mainly by extensive comparative laboratory testing, and not to re-establish efficacy and safety, as these have already been established for the originator.

As part of the assessment process, biosimilars must demonstrate that they are highly similar to an already approved originator biological medicine.² A biosimilar must be shown to be highly similar to the originator in quality and biological activity, with no clinically meaningful differences in efficacy, safety and immunogenicity. The foundation of evidence for similarity is provided by the extensive laboratory comparability studies between the biosimilar and the originator, including physicochemical and structural properties, biological activity and functional in vitro studies. Biologicals are often large and complex molecular structures; therefore, comparability studies use highly sensitive state-of-the-art analytical technology that allows robust and extensive examination and comparison of the biosimilar and originator molecules. These comparability studies are required in addition to the comprehensive pharmaceutical quality information.

A full clinical development programme is not necessary when extensive laboratory testing has demonstrated that the biosimilar is highly similar to the originator. The purpose of clinical studies in a biosimilar development programme is to help address remaining questions that require human data to evaluate, such as pharmacokinetics. In addition, a comparative efficacy study is commonly used to confirm there are no clinically meaningful differences. Once a biosimilar is demonstrated to be highly similar to the originator with no clinically meaningful differences, it can be approved for the same indications as the originator on the basis of the established efficacy and safety of the originator in each indication. This avoids the unnecessary repetition of clinical trials.

Biosimilars have been used safely for many years. The safety of all medicines on the market, including biosimilars, is monitored to protect patients (pharmacovigilance). Regulators have not identified any relevant differences in the type, severity or frequency of side effects between biosimilars and their respective originators.

Globally, regulators have confidence in the rigour of the scientific review and approval process for biosimilars.

Although regulatory pathways for biosimilar licensing differ across countries, the various pathways are robust, as demonstrated by up to 13 years of use throughout the world. Many biosimilars are approved for a wide range of indications, including somatropin, epoetin, filgrastim, pegfilgrastim, follitropin alfa, insulin glargine and insulin lispro, infliximab, etanercept, rituximab, trastuzumab, adalimumab, bevacizumab (not all biosimilars are available in all markets).

Biosimilars enhance competition among biological medicines, providing more treatment alternatives for patients and clinicians. The increased market competition has the potential to reduce pricing of biologicals, enabling improved access to biological medicines for a larger number of patients.

Biosimilars have been increasingly used in clinical practice in most countries. Many regulatory agencies, healthcare providers and clinician associations accept that there are no clinically meaningful differences between biosimilars and originators and that biosimilars are safe and effective treatment options that can be equally prescribed to patients. In particular, changing between originator and biosimilar (i.e., a prescribing healthcare professional transferring a patient on treatment from one medicine to another) is an accepted clinical practice in many countries. Some countries have regulatory frameworks that permit substitution at the pharmacy level (i.e. without intervention by the prescriber) under certain conditions.

Note:

The legal and regulatory framework applicable in each country governs biosimilars in that country. However, legal and regulatory differences across countries or regions do not affect the general principles expressed in this statement.

There are copy products in some countries that have not been approved on the basis of a robust biosimilar regulatory pathway, as described above. It should be emphasised that these 'copy products' or 'non-comparable biologics' have not gone through extensive comparability studies and cannot be considered as biosimilars. Any questions should be addressed to the National Regulatory Authority for the relevant country.

¹ Biosimilars are also called biosimilar products, biosimilar medicines, similar biological medicinal products or similar biotherapeutic products (SBPs).

² Originator (original brand product or medicine) is also referred to as a reference product or reference medicine.

¹ ICMRA is an international executive-level coalition of key regulators from every region in the world. It provides a global strategic focus for medicines regulators and gives strategic leadership on shared regulatory issues and challenges. Priorities include coordinated response to crisis situations. Members of the ICMRA include: Therapeutic Goods Administration (TGA), Australia; National Health Surveillance (ANVISA), Brazil; Health Products and Food Branch, Health Canada (HPFB-HC), Canada; China National Medical Products Administration (NMPA), China; European Medicines Agency (EMA) and European Commission - Directorate General for Health and Food Safety (DG - SANTE), European Union; French National Agency for Medicines and Health Products Safety (ANSM), France; Paul-Ehrlich-Institute (PEI), Germany; Health Product Regulatory Authority (HPRA), Ireland; Italian Medicines Agency (AIFA), Italy; Ministry of Health, Labour and Welfare (MHLW) and Pharmaceuticals and Medical Devices Agency (PMDA), Japan; Ministry of Food and Drug Safety (MFDS), Korea; Federal Commission for the Protection against Sanitary Risks (COFEPRIS), Mexico; Medicines Evaluation Board (MEB), Netherlands; Medsafe, Clinical Leadership, Protection & Regulation, Ministry of Health, New Zealand; National Agency for Food Drug Administration and Control (NAFDAC), Nigeria; Health Sciences Authority (HSA), Singapore; Medicines Control Council (MCC), South Africa; Medical Products Agency, Sweden; Swissmedic, Switzerland; Medicines and Healthcare Products Regulatory Agency (MHRA), United Kingdom; Food and Drug Administration (FDA), United States and the World Health Organization as an observer. Associate members include Austrian Medicines and Medical Devices Agency (AGES), Danish Medicines Agency, Israel Office of Medical Technology, Health Information and Research (MTHIR), Poland Office of Registration of Medicinal Products and Biocidal Products (URLWMIPIB), Russia Roszdravnadzor and Spain Agencia Española de Medicamentos y Productos Sanitarios (AEMPS)

LIST OF DEAR HEALTHCARE PROFESSIONAL LETTERS ON SAFETY CONCERNS ISSUED BY HSA, PHARMACEUTICAL AND MEDICAL DEVICE COMPANIES (1 MAY 2019 TO 31 AUG 2019)

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

Therapeutic products

9 May 2019	Implanon NXT® (etonogestrel) Update to the insertion and removal instructions in Local Product Circular to minimise the risk of intravascular insertion and neurovascular injury
27 May 2019	Soluvit™ N (biotin) Potential interference of biotin with clinical laboratory tests that are based on biotin/streptavidin interaction, leading to incorrect laboratory values
24 Jun 2019	Lemtrada (alemtuzumab) Risks of immune-mediated reactions and serious cardiovascular adverse events occurring in close temporal association with Lemtrada infusions
1 Jul 2019	DARZALEX® (daratumumab) New risk of Hepatitis B reactivation and recommendations for HBV screening
23 Jul 2019	Hydrochlorothiazide Update on HSA's review regarding the risk of non-melanoma skin cancer associated with hydrochlorothiazide use

Medical devices

6 May 2019	Xenform™ Soft Tissue Repair Matrix, Uphold™ Lite with Capio SLIM Vaginal Support System, Polyform™ Synthetic Mesh and Pinnacle™ LITE Pelvic Floor Repair Kit, Posterior Worldwide withdrawal due to insufficient clinical evidence to assure that the benefits outweigh the probable risks. Currently, only the Uphold™ Lite with Capio SLIM Vaginal Support System is registered in Singapore.
10 May 2019	Breast implants Notification of potential risk of breast implant-associated anaplastic large cell lymphoma and advisory for appropriate clinical management
12 May 2019	MitraClip XTR Clips Notification of non-functionality of the clips due to unintended excessive force applied to them during implantation
14 May 2019	Azure™ and Astra™ pacemakers, and Percepta™, Serena™ and Solara™ cardiac resynchronization therapy pacemakers Notification of potential serious failure mode in a subset of devices due to the internal cracking within these capacitors resulting in the development of leakage pathways, causing high current drain and rapid battery depletion
31 May 2019	Medtronic HeartWare Monitor AC Adapter Notification of potential damage under electric current surge conditions
13 Jun 2019	UNI-Graft® K DV vascular prostheses straight tube 12mm diameter 15cm length Alert on product counterfeit and advisory to check for correct packaging before use
1 Jul 2019	Covidien Endo GIA articulating reloads with Tri-Staple technology Voluntary recall of selected lots due to the potential risk of the device missing one of two pin components that maintain alignment of the device jaws
11 Jul 2019	Equistream®, Equistream® XK, and GlidePath® long-term hemodialysis catheters Voluntary recall of selected lots as they may be at risk of containing a tunneler with a plastic barb tip that is susceptible to breakage
31 Jul 2019	Apollo BIB and Orbera IntraGastric Balloon Systems Updates to the Instructions for Use to include residual risks of gastric and esophageal perforation, the warnings and precautions related to pregnancy and patients at higher risk of aspiration, and clarification on an existing warning on bowel obstruction
7 Aug 2019	Natrelle BIOCELL® textured breast implants and BIOCELL® textured tissue expanders Voluntary recall of affected devices due to uncommon incidence of breast implant-associated anaplastic large cell lymphoma and advisory to cease implantation of affected devices
28 Aug 2019	Medtronic Micra™ Delivery System Update to the Instructions for Use on tether removal during implant



continued from page 5

Answer

Q1: b. False.

Not all product defects will pose a serious threat to the intended users, cause an illness or affect the outcome of a person's medical treatment. Some examples include dented shipping cartons, and minor typographical errors on the product label which does not affect critical information such as the strength of the product, the dose, the name of the product, etc.

Q2: a. True.

To ensure that product defects are promptly investigated, importers of therapeutic products (TP) are required to report product defects to HSA. This includes product defects for unregistered TPs for patients' use that have been imported into Singapore by healthcare institutions. Such product defects should be reported to HSA by the healthcare institution who had imported the unregistered TP or the company who had imported the product on behalf of the healthcare institution. Any defect which presents a serious threat to persons or public health must be reported to HSA within 48 hours of the reporter becoming aware of the defect. For other cases, the defect will need to be reported within 15 calendar days.

Q3: g. Any of the above.

Depending on the risk associated with the product defect and the potential impact to the quality, safety and efficacy of the product, appropriate measure(s) will be taken to mitigate the risk to the patients. For example, if the product defect can result in safety or efficacy issues, the product may be recalled from the market. A Dear Healthcare Professional Letter may be issued to inform healthcare professionals on the product defect and provide advice on risk mitigation measure(s). For product defects that are due to manufacturing process issues, the company would be required to make the appropriate changes to the manufacturing process to prevent future occurrence of defects.

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.



ANSWERS TO AE CASE IN FOCUS: TEST YOURSELF

Possible mechanisms

The chronology of events suggests that the calcium gluconate infusion precipitated the ischemic symptoms. It is hypothesized that the calcium gluconate resulted in vasodilation (likely systemic), which on the background of reduced baseline perfusion from the subclavian occlusion, precipitated a relative arm ischemia. This is similar to the way arm exercises can precipitate ischemia in patients with subclavian occlusion. When asked, the patient denied previous symptoms of arm claudication (potentially because he does not usually exert himself) or vertebrobasilar insufficiency*. On subsequent follow-up, his hand remained pink and warm without any need for intervention.

Other mechanisms, such as extravasation and vasospasm, were also considered. While it was possible that there was some extravasation of the drug into the soft tissue, the extent was fairly minor and there was no dermal necrosis noted by the plastic surgeon. The lesions were treated conservatively and resulted in full and rapid recovery. The possibility of calcium gluconate precipitating cutaneous vasospasm was also proposed, but this has not been described before and is somewhat counter-intuitive as calcium is known to be vasodilatory. Vasospasm is also expected to be more localised distally in the digits and hand rather than extending up into the forearm.

Discussion

Intravenous calcium gluconate is indicated for cardiac stabilization in the management of hyperkalaemia with associated ECG changes, as well as the treatment of acute symptomatic hypocalcaemia. Rapid infusion of calcium gluconate is known to cause vasodilation, hypotension, bradycardia, arrhythmias, syncope and even cardiac arrest. It is possible that the calcium gluconate infusion in the left arm caused abrupt vasodilation, and along with the pre-existing diminished hand perfusion, resulted in vascular insufficiency with symptoms of limb ischaemia. In addition, any pre-existing intracranial or extracranial arterial vascular disease may have contributed to the loss of compensation by the reversed ipsilateral vertebral blood flow.¹

The treating physicians of this patient opined that it is important to consider intravenous calcium gluconate as potentially hazardous to patients with subclavian artery stenosis if there is a possibility of inducing arm ischaemia and propose a simple way to mitigate this risk. The simplest method is to administer the drug centrally. However, if this is not possible and should unequal pulses or blood pressures be found between the two upper limbs, then the treating physicians suggest that the drug be administered through the limb with the stronger pulse or higher blood pressure.

This is the first report received by HSA of possible acute upper limb ischaemia secondary to SSS precipitated by intravenous calcium gluconate infusion. It is also, to the best of our knowledge, the first reported case of pharmacologically-induced SSS. HSA would like to encourage all healthcare professionals to continue reporting adverse events, as our partnership is an important cornerstone in drug safety monitoring.

References

1. *Am J Surg* 1994; 168: 91-3

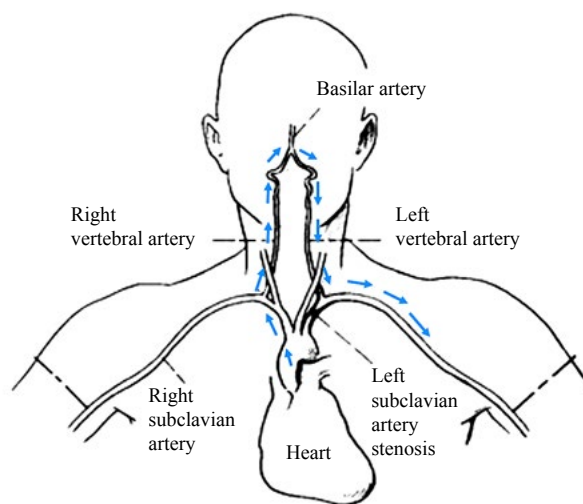
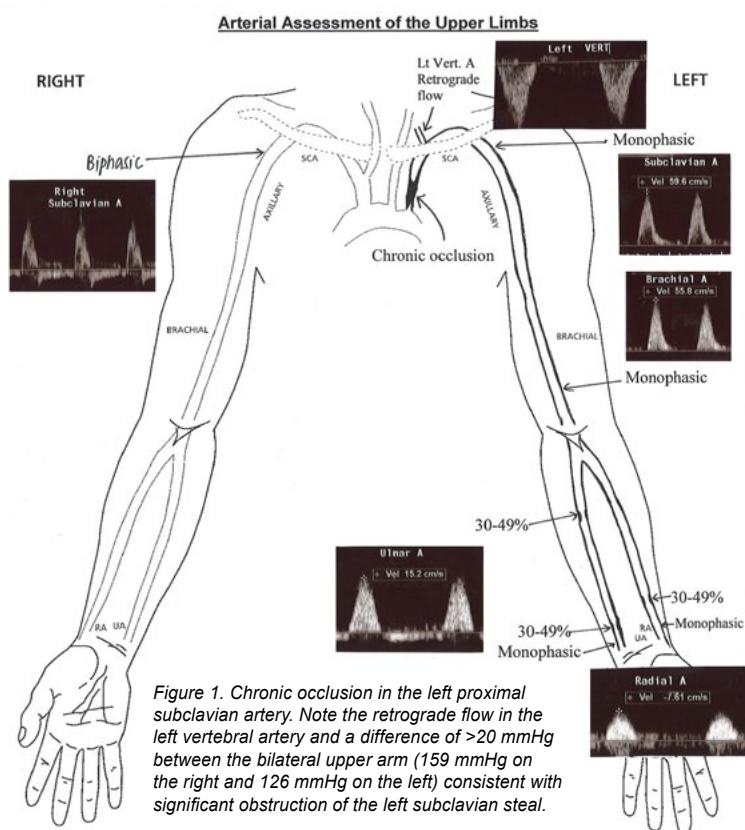


Figure 2. Subclavian steal syndrome. Occlusion of the left subclavian artery proximal to the origin of the vertebral artery, resulting in retrograde flow in the left vertebral artery (blue arrows).

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