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ADVERSE DRUG REACTION NEWS

HSA Health Sciences Authority

Health Product Safety Information Summary

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This is a case of a 78-year-old female with type 2 diabetes mellitus (DM) and diabetic macular oedema who was started on aflibercept, a monthly intravitreal anti-vascular endothelial growth factor (anti-VEGF). She was also taking gliclazide for type 2 DM, amlodipine, valsartan and spironolactone for hypertension and heart failure with preserved ejection fraction, as well as donepezil for Alzheimer's disease. Five months after initiation of intravitreal aflibercept, she developed renal impairment. Her serum creatinine worsened gradually to 560 umol/L in the next four months. At the ninth month, her urinalysis showed zero red blood cells, while her urine protein-creatinine ratio was high at 3.19 mg/mg. An ultrasound of the kidneys, ureters and bladder showed increased parenchymal echogenicity of both kidneys and no obstructive lesions. No renal biopsy was done.

What could have caused the renal impairment in this patient?

Published by the Health Products Regulation Group, HSA and the HSA Product Vigilance Advisory Committee

List of Dear Healthcare Professional Letters on therapeutic product safety concerns issued by HSA and pharmaceutical companies in 2024

For details of each DHCPL, please log on to MOH Alert via your professional board's website.

Date of issuance	Therapeutic product safety concern
23 January 2024	**Epilim® (valproate)** Updates and new measures related to the risk of neurodevelopmental disorders in children of fathers treated with valproate
1 February 2024	**NovoMix® 30 FlexPen® 100U/ml 3ml 5s** **Insulatard® HM Penfill® 100IU/ml 3ml 5s** **NovoRapid® Flexpen® 100U/ml 3ml 5s** Cracked cartridges found in batches from cartridge supplier and used for filling of insulin products
18 March 2024	**Zyrtec-D (cetirizine/ pseudoephedrine)** Risks of posterior reversible encephalopathy syndrome and reversible cerebral vasoconstriction syndrome associated with the use of pseudoephedrine
4 July 2024	**NovoSeven® 2mg (eptacog alfa)** Potential product deviation resulting in under-filling of the product
12 August 2024	**Tecentriq (atezolizumab) and Avastin (bevacizumab)** Tecentriq (atezolizumab) in combination with Avastin (bevacizumab) is not approved as adjuvant therapy in patients with hepatocellular carcinoma at high risk of recurrence after surgical resection or ablation and the benefit-risk profile does not support their use in this setting
13 September 2024	**Lunsumio (mosunetuzumab)** New important identified risk of hemophagocytic lymphohistiocytosis
19 September 2024	**Plaquenil® (hydroxychloroquine sulfate)** Risk of major congenital malformations and new risks of phospholipidosis and aggravation of myasthenia gravis symptoms
26 September 2024	**Imbruvica® (ibrutinib)** New identified risk of hepatotoxicity (including hepatic failure) in treated patients
17 October 2024	**Tegretol Oral Suspension 2%** Updates to the posology, method of administration, and limitation of use in neonates to restrict intake of sorbitol or propylene glycol
29 October 2024	**Gavreto® (pralsetinib)** New warning and precaution of severe and fatal infections
7 November 2024	**Topamax® (topiramate)** Safety measures to prevent exposure during pregnancy

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.

Dear Healthcare Professional Letters on safety concerns

Scan/click on QR code

How to report suspected AEs to HSA?

For any suspected AEs, please report to us via the following:

HSA_productsafety@hsa.gov.sg

https://www.hsa.gov.sg/adverse-events

For any enquiries or assistance on AE reporting, please call us at 6866 1111

All website references were last accessed on 1 May 2025.

mRNA COVID-19 vaccine safety update: Insights from nationwide surveillance

Key Points

- Active surveillance for the monitoring of COVID-19 mRNA vaccines adverse events (AEs) was rolled out during the COVID-19 pandemic period.
- Eight adverse events of special interests (AESIs) were identified and assessed, with three safety signals detected: myocarditis/pericarditis, cerebral venous thrombosis and appendicitis.
- Active surveillance by HSA and AE reporting by healthcare professionals are critical components of safety surveillance. AE reports serve as a primary source of initial suspicion, triggering subsequent investigative actions. Healthcare professionals are strongly encouraged to report suspected AEs with health products to HSA.

HSA's pharmacovigilance programme has progressively integrated active surveillance capabilities to investigate safety concerns involving medicines using anonymised electronic health records (EHRs). Active surveillance using deidentified EHR data involves proactively obtaining and analysing data from healthcare systems to verify safety signals identified through passive surveillance.[1] This means that we can use tools to plough through EHRs to investigate the link between medicines and adverse events (AEs). Active surveillance has been applied to investigate adverse events of special interest (AESIs) relating to COVID-19 mRNA vaccines during the COVID-19 pandemic. This article provides an update on the serious AEs associated with monovalent COVID-19 mRNA vaccines, administered as primary series and first booster vaccination which HSA had investigated using EHRs. These findings contribute to the evolving understanding of the safety profile of mRNA vaccines with ongoing surveillance.[1]

Adverse events of special interest (AESIs)

At the time of analysis (mid-September 2022), approximately 5 million people had received two doses of an mRNA vaccine, of which 87 % (4.2 million) had also received a subsequent booster dose. HSA received a total of 11,717 AE reports associated with mRNA vaccines by the end of August 2022, which formed the basis for our safety investigations.

Attention was placed on safety concerns raised and prioritised by other health authorities along with signals of local public concern. Factoring in feasibility of investigation with the data available in EHRs, the following eight AESIs were identified for active surveillance in the local population aged 5 years and above:

- Myocarditis/pericarditis
- Cerebral venous thrombosis (CVT)
- Appendicitis
- Strokes (ischaemic and haemorrhagic combined)
- Myocardial infarction (MI)
- Seizures and convulsions
- Pulmonary embolism
- Immune thrombocytopenia

Using 'Observed-over-Expected' (O/E) and Self-Controlled Case Series (SCCS) methodologies for signal investigation

As part of the investigations, expected population rates in the post-vaccination years of 2021 and 2022 were estimated using historical data (from 2018, 2019 and 2020) for all eight AESIs. These expected rates were compared against actual event rates seen during the 42-day post-vaccination period [termed 'observed-over-expected' (O/E) analysis]. O/E comparisons were conducted in age-sex stratified subpopulations. Statistical significance alone does not necessarily indicate causality. Therefore, when observed AESI rates significantly exceed expected rates, it signals the need for further investigation. Formal epidemiological studies such as self-controlled case series (SCCS) analyses were then performed for a more thorough investigation of the signals (Figure 1). By design, the SCCS represents a markedly different approach to investigating a safety concern in comparison to the O/E. The SCCS considers the timing of an AESI's occurrence in each individual and whether the aggregated event rates across all observed cases in the 42-day post-vaccination risk window is higher than that of control periods outside the risk window. The method allows for individual-level confounder control and adjustments are also made to minimise potential biases, through seasonal variation in the AESI and the influence of event occurrence on subsequent vaccination behaviour.

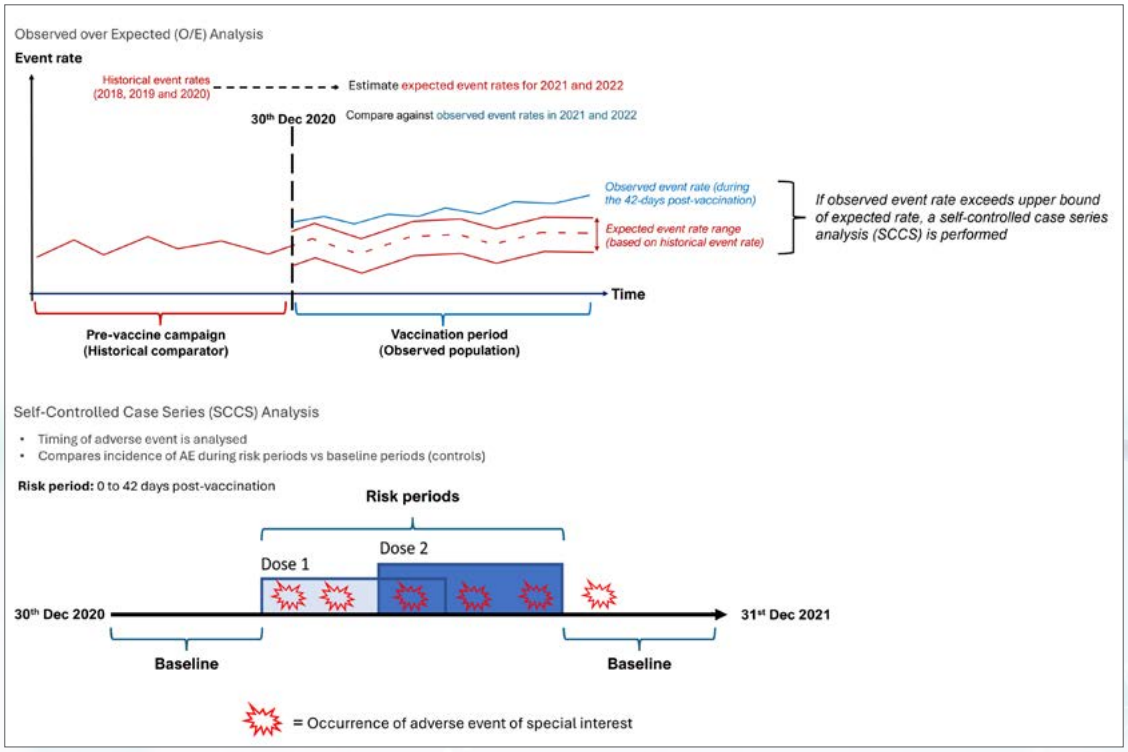

Figure 1. Overall strategy in identifying safety signals relating to COVID-19 mRNA vaccines with Observed-over-Expected analysis conducted first for screening and Self-controlled Case Series analysis performed for validation

Results

Three out of the eight AESIs studied showed increased risks post-vaccination on both O/E and SCCS analyses: myocarditis/pericarditis, CVT and appendicitis. In contrast, no increased risk was observed for strokes, MIs and other AESIs investigated in the adult population. No increased risks of seizures/convulsions, appendicitis and myocarditis/pericarditis were observed in the paediatric population aged 5 to 11 years.

Summary of key findings

Myocarditis/Pericarditis: An elevated risk was observed, particularly following the second dose of mRNA COVID-19 vaccines. Males aged 12 to 17 years were at the highest risk of this AE, with the data suggesting approximately one additional case per 20,000 in this subgroup. The risk progressively decreases with increasing age and no significant risk elevation was observed among those 50 years and above. While the risk remains elevated with booster dose one, the risk appears lower than that observed after the second dose. In general, cases of vaccine-induced myocarditis/pericarditis have been mild, with most patients making good recoveries. In terms of longer-term cardiovascular sequalae, recent evidence from the literature suggests that about 5 to 10 % of patients experience rehospitalisation for cardiac events (approximately 4 % for myocarditis/pericarditis) within 18 months of the initial post-vaccination myopericarditis admission.[2] It is important to note that COVID-19 infections carry substantial risks of myocarditis/pericarditis, which was reported to be more than seven-fold higher than in those who received the COVID-19 vaccine.[3]

Cerebral Venous Thrombosis (CVT): Our findings suggested that approximately one additional case may be attributed to mRNA vaccination per 500,000 persons vaccinated. This risk appears to peak during the first two weeks following dose two (or four to five weeks post-dose one). Males aged above 50 years appear to be at the highest risk, accounting for 11 out of 16 cases (69 %) observed within 42 days of vaccination. No increased risk was observed with booster dose one.

Appendicitis: An increased risk was observed particularly among adolescents aged 12 to 17 years. Adolescent males appeared to experience a higher risk after dose one whereas among adolescent females, the risk increased after dose two, resulting in one additional case per 50,000 adolescents in aggregate. Notably, an elevated risk of appendicitis was observed in the vaccine arm of a Phase III clinical trial and in post-marketing safety data.[4,5] However, no increased risk was observed with booster doses.

Strokes and MIs: Our active surveillance did not detect an elevated risk of stroke (ischemic and haemorrhagic combined) or MI following COVID-19 mRNA vaccination.

Five to 11-year-olds: No increased risks of seizures/convulsions, appendicitis and myocarditis/pericarditis was observed amongst paediatric vaccine recipients aged 5 to 11 years receiving the primary series vaccination.

Conclusion

Active surveillance using deidentified EHRs has heralded a new era of pharmacovigilance as evidenced by our pilot work on COVID-19 mRNA vaccines. We identified increased risks of myocarditis/pericarditis, CVT and appendicitis when the vaccines were administered as part of the primary vaccination series in our local population. Active surveillance also allows for the generation of real-world evidence to inform periodic benefit-risk re-assessments. This ensures that the anticipated benefits of any health product outweigh its potential harms in relevant subgroups of the population throughout the product life cycle. Despite this, we cannot undermine the importance of AE reporting which remains the cornerstone of pharmacovigilance and a shared responsibility between HSA and healthcare professionals. It is usually through the initial suspicion of healthcare professionals reporting AEs that trigger subsequent investigative actions using real-world data, to validate the safety signal. Healthcare professionals are strongly encouraged to report suspected AEs for all health products to the HSA Vigilance and Compliance Branch.

References

1. *Vaccine: X 2023; 15: 100419*
2. *JAMA 2024; 332(16): 1367-77*
3. *Front Cardiovasc Med. 2022; 9: 951314*
4. *Drug Saf 2024; 47: 1157-69*
5. *N Engl J Med 2020; 383: 2603-15*

Analysis of adverse event reports for year 2024

Key Points

- In 2024, HSA received 25,141 valid adverse event (AE) reports.
- The top pharmacotherapeutic product groups suspected of causing AEs were antibiotics, nonsteroidal anti-inflammatory agents, analgesics, antithrombotic agents and antidiabetic agents, similar to the previous year.
- There were 447 vaccine adverse event (VAE) reports, including 66 COVID-19 VAE reports. The commonly reported AEs with childhood vaccines in children below 12 years included lymphadenopathy (suppurative and non-suppurative) and injection-site reactions with the *Bacillus Calmette-Guérin* (BCG) vaccine and seizures (febrile and afebrile) with various vaccines. The commonly reported VAEs in adults were allergic reactions and injection site reactions.
- There were 83 AE reports associated with complementary health products (CHPs) and cosmetics. Most of the AEs were allergic reactions with glucosamine-containing products and melatonin.

This is a review of AE reports received by HSA in 2024. The scope of this review includes pharmaceuticals (i.e., chemical drugs, biologics, vaccines), cell, tissue, and gene therapy products (CTGTP), complementary health products (CHPs) and cosmetic products.

Report analysis for 2024

(a) Volume of reports

In 2024, HSA received a total of 25,141 valid[+] reports. This figure is higher than the average annual volume of 24,161 reports received for the past 10 years (i.e., 2014 to 2023) and close to the 25,637[+] reports received in 2023.

+ Reports include COVID-19 vaccine AE reports. Reports lacking important details such as names of suspected drugs and AE descriptions were regarded as invalid reports and were not captured into the national AE database as these could not be assessed for causality.

(b) Types and sources of reports

Majority of the reports were associated with pharmaceuticals (99.6 %), which included chemical drugs (95.9 %), vaccines (2.4 %), and biologics (1.3 %). This was followed by CHPs (0.3 %), which included Chinese Proprietary Medicines, health supplements and traditional medicines. The remaining reports were associated with CTGTP (0.05 %) and cosmetic products (0.02 %).

Most of the AE reports were from public hospitals (39.3 %), followed by General Practitioner (GP) clinics (37.8 %) and polyclinics (17.6 %). GP clinics continue to be among the top contributors for AE reports since 2023. This correlates with the GP clinics' ongoing integration with the National Electronic Health Records (NEHR) system. Other reporting sources included private specialist clinics (2.5 %), product registrants (1.9 %), private hospitals (0.4 %) and government agencies (0.2 %). Doctors (91.9 %) contributed the highest number of reports, followed by pharmacists (3.4 %). The remaining groups of reporters were dentists, nurses and research coordinators.

(c) Demographics

Where patient demographics were reported, two-thirds of the AE reports received were for females (61.6 %). Chinese patients constituted the highest proportion (75.4 %) of AE reports, followed by Malays (13.6 %), Indians (7.2 %), Eurasians (0.3 %) and others (3.5 %). The majority of AEs occurred in adults (18 years and above, 93.5 %), followed by children (below 12 years, 3.9 %) and adolescents (12–17 years, 2.6 %).

AE reports associated with chemical drugs, biologics and CTGTP

The top five drug classes suspected of causing AEs were from the following pharmacotherapeutic groups: antibiotics (42.7 %), nonsteroidal anti-inflammatory drugs (NSAIDs) (27.3 %), analgesics (11.5 %), antithrombotic agents (5.3 %) and antidiabetic agents (4.5 %). Refer to Figure 1 for the breakdown of the top three drugs within each of the top five drug classes.

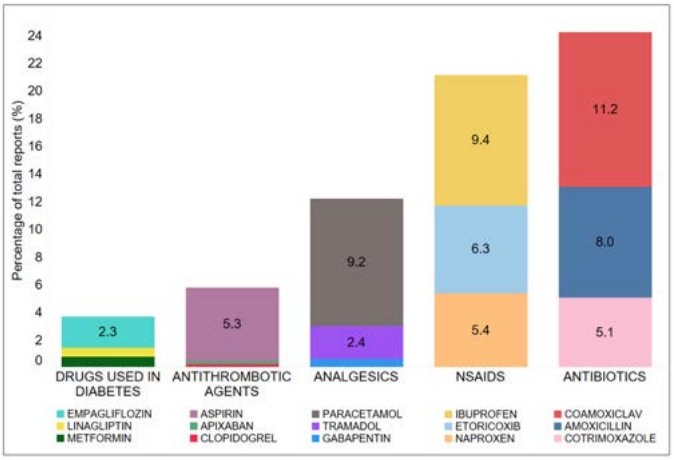

Figure 1. Top 5 drug classes and the top 3 drugs within each drug class (by active ingredients) suspected of causing AEs

A large proportion of AEs reported were skin and subcutaneous tissue disorders (63.5 %), followed by eye disorders (e.g., periorbital oedema, oculogyric crisis, red eye) (11.1 %) and general disorders and administration site conditions (e.g., generalised oedema, chest discomfort, weakness) (7.6 %). Most of the AE reports described non-serious reactions such as rash, pruritus, angioedema, and dyspnoea. The top five active ingredients suspected to cause serious AEs of interest in 2024 are summarised in Table 1.

It is worth noting that these figures do not take into consideration the drugs' utilisation rates and therefore do not inform on their relative safety profiles. More than one drug may be implicated in a single AE report. Overall, the AEs associated with the implicated drugs are generally consistent with the known safety profile of these drugs.

Vaccine AE reports

HSA received 447 vaccine adverse event (VAE) reports in 2024, including 66 (14.8 %) reports associated with COVID-19 vaccines*. Of these, 175 (39.1 %) reports involved adults and 272 (60.9 %) reports involved children and adolescents aged 18 and below. Most of the reports in children and adolescents were received from the active surveillance site at KK Women's and Children's Hospital (n=255, 93.8 %), which HSA partners to screen paediatric hospital admissions for AEs post-vaccination.

**COVID-19 vaccines include mRNA vaccines (Comirnaty® and Spikevax®), protein subunit vaccine (Nuvaxovid®) and inactivated vaccine (Sinovac-CoronaVac®).*

(a) VAEs in children and adolescents

The commonly reported VAEs in children below 12 years were lymphadenopathy (suppurative and non-suppurative) and injection-site reactions with the *Bacillus Calmette-Guérin* (BCG) vaccine and seizures (febrile and afebrile) with various vaccines. Seizures were most frequently reported with pneumococcal conjugate, measles, mumps and rubella (MMR), measles, mumps, rubella and varicella (MMRV), varicella, 6-in-1^ and influenza vaccines. Other VAEs reported for this age group included allergic reactions such as rash and urticaria, *Henoch-Schönlein* purpura, thrombocytopenia, meningitis and Kawasaki disease.

Table 1. Top active ingredients suspected to cause serious AEs of interest in 2024, in comparison to the period 2020 to 2024*

Description	Top 5 suspected active ingredients in 2024	Top 10 suspected active ingredients from 2020-2024. (Based on cumulative number of times the active ingredients were implicated from 2020-2024)
Severe cutaneous adverse reactions (SCARs) (Acute generalised exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN))	COAMOXICLAV 31 COTRIMOXAZOLE 23 PIPERACILLIN AND TAZOBACTAM 14 VANCOMYCIN 13 ETORICOXIB 10 CEFAZOLIN 10 AMOXICILLIN 10	COAMOXICLAV 115 COTRIMOXAZOLE 85 ALLOPURINOL 71 OMEPRAZOLE 61 PIPERACILLIN AND TAZOBACTAM 47 VANCOMYCIN 38 AMOXICILLIN 36 CEFAZOLIN 34 ETORICOXIB 32 MEROPENEM 30 LEVOFLOXACIN 30
Anaphylactic Reaction	COAMOXICLAV 31 PARACETAMOL 30 IBUPROFEN 29 ASPIRIN 29 DICLOFENAC 27	COAMOXICLAV 150 IBUPROFEN 145 PARACETAMOL 117 DICLOFENAC 117 NAPROXEN 97 ASPIRIN 91 AMOXICILLIN 73 CEFAZOLIN 72 IOHEXOL 57 ATRACURIUM 56
Renal disorders (Renal Tubular Disorder/Necrosis, Renal Failure Acute/Chronic, Glomerulonephritis, Nephritis Interstitial, Toxic Nephropathy, Nephrosis, Autoimmune renal disease)	CIPROFLOXACIN 9 PEMBROLIZUMAB 2 PARACETAMOL 2 OMEPRAZOLE 2 NAPROXEN 2 DICLOFENAC 2	CIPROFLOXACIN 43 DICLOFENAC 15 OMEPRAZOLE 13 ETORICOXIB 9 COAMOXICLAV 8 ATORVASTATIN 8 PEMBROLIZUMAB 7 PARACETAMOL 7 ACICLOVIR 6 NIFEDIPINE 5 LOSARTAN 5 DAPAGLIFLOZIN 5
Hepatic disorders (Jaundice, Hepatic Coma, Hepatic cirrhosis, Hepatitis, Hepatitis Cholestatic, Hepatic Failure, Hepatocellular Damage, Liver Injury)	ATORVASTATIN 25 COAMOXICLAV 11 ALLOPURINOL 5 SIMVASTATIN 4 ROSUVASTATIN 4 COTRIMOXAZOLE 4	ATORVASTATIN 59 COAMOXICLAV 39 COTRIMOXAZOLE 13 CARBIMAZOLE 11 AZATHIOPRINE 9 SIMVASTATIN 8 ALLOPURINOL 7 ROSUVASTATIN 6 PARACETAMOL 6 HYDRALAZINE 6

**More than 5 or 10 active ingredients may be displayed in each column respectively if the number of reports of these active ingredients is the same.*

VAEs in adolescents aged 12–17 years included reports of rash and urticaria with various vaccines, such as MMR and influenza vaccines, palpitations, chest pain or discomfort with COVID-19 vaccines and isolated reports of angioedema and appendicitis with COVID-19 vaccines.

^6-in-1 refers to Diphtheria, Pertussis, Tetanus, Inactivated Polio, Haemophilus Influenza Type B and Hepatitis B

(b) VAEs in adults

The commonly reported VAEs in adults were allergic reactions such as rash, urticaria, angioedema and injection site reactions. Serious VAEs included anaphylaxis with tetanus toxoid, COVID-19 and hepatitis A/B vaccines, and autoimmune hepatitis with COVID-19 vaccines. There were also isolated reports of encephalitis and Guillain-Barré syndrome with Zoster vaccine, as well as syncope and relapsed minimal change disease with COVID-19 vaccine.

HSA's review of the VAE reports in 2024 did not identify new safety concerns with the vaccines. Overall, the VAEs received in 2024 were within the expected AE frequencies listed in the product package inserts or reported in literature.

Complementary health products and cosmetics AE reports

There were 83 AE reports associated with CHPs and cosmetics, with 52 (62.7 %) cases implicating products classified as health supplements. Majority of the CHP reports were associated with glucosamine-containing products (n=26, 31.3 %) and melatonin (n=9, 10.8 %). AEs reported were primarily allergic reactions, such as rash and pruritus.

Serious AEs reported with CHPs were rare and included hepatic AEs and anaphylaxis. There was no safety concerns identified for these CHPs, as these were isolated cases and some were confounded by multiple factors such as the patient's underlying conditions and/or concomitant use of other products.

Several products containing adulterants or toxic heavy metals were detected through AE reports, including:

- "Sausando Cellulite Pills", which contained sibutramine, phenolphthalein and frusemide, led to seizures and hyponatraemia in a male patient.
- "Natural Herbs", which contained dexamethasone, resulted in Cushing's syndrome in a female patient.
- "La Mu Cao Capsules", which contained prednisolone, amoxicillin, diclofenac and paracetamol, provided unusually quick relief for a female consumer's leg pain.
- "ayukalp Mahayograj Guggulu", which contained lead exceeding 6,000 times the permissible limit, resulted in lead poisoning in a female patient.
- "88 Total White Underarm Cream", which contained mercury, betamethasone and salicylic acid, caused a female patient to develop allergic contact dermatitis and drug reaction with eosinophilia and systemic symptoms (DRESS) due to mercury exposure.
- "Touch Skin by DermaCare Skin Relief Treatment Cream", which contained betamethasone valerate, caused a female patient's skin to be severely inflamed and photosensitive when she abruptly stopped the cream after using it for 8 years. She also experienced skin atrophy with telangiectasia.

HSA also received three AE reports associated with counterfeit "LACTOGG" capsules, which were marketed as probiotics. Two adults experienced gastrointestinal symptoms while a toddler experienced high fever and abnormally coloured faeces. HSA's analysis revealed that the consumers' sample did not contain the probiotic strain, *Lactobacillis rhamnosus GG*, which is present in the genuine product.

Press releases[1] were issued to warn the public not to purchase and use these products.

Highlights on Local Safety Signals for the Year 2024

HSA conducts regular individual and aggregated review of all adverse event (AE) reports. This aims to detect two categories of AEs: serious unexpected AEs not listed in the drug's package insert (PI), and known AEs reported more frequently than observed from clinical trials or global post-marketing experience. Any local safety signals and significant drug-AE pair of interest relevant to the local context will be published in this bulletin to raise awareness of healthcare professionals. These signals may be preliminary investigations and may not necessarily mean that there is a confirmed safety issue with the drug.

In 2024, the following local safety signals were identified by HSA:

Breakthrough seizures following brand switch with levetiracetam

HSA was alerted to eight reports of breakthrough seizures associated with levetiracetam from two healthcare institutions in 2024. This occurred in patients who switched to Levipil tablets or Levetiracetam-AFT oral solution from other brands of levetiracetam, including both innovator and generic products. Prior to this, HSA received an annual average of one to three reports of breakthrough seizures with levetiracetam in the previous five years.

Of the eight reports received, four involved children aged 5 to 12 years, while the remaining four were adults. The children were subsequently switched back to their previous brands of levetiracetam and had no further breakthrough seizures. Of the four adult cases, two had their doses of Levipil increased after their breakthrough seizures and were subsequently maintained on Levipil. One patient switched to another brand of levetiracetam but still had seizures. The last patient remained on the same dose of Levipil as she was not keen to increase her dose due to the side effect of tiredness and did not have further seizure recurrence.

As part of HSA's investigations, information (including Certificates of Analysis[a]) was gathered from the product registrants for review and these did not indicate any product quality issues for the affected batches. Samples of the affected batches were sent for testing and found to be in order. Other possible factors for breakthrough seizures include the patient's underlying condition (e.g., refractory seizures) and non-compliance to medications or administration issues (e.g., crushing of tablets prior to administration via nasogastric tube). Following this, no further cases of breakthrough seizures associated with switching of levetiracetam brands were reported to date.

[a]Documents with details of laboratory tests conducted to verify a specific batch meets defined quality standards

Anaphylaxis with Iohexol

Iohexol (Omnipaque™, GE Healthcare Pte. Ltd.) is an X-ray contrast medium for diagnostic imaging. During a routine review of the AE database, it was noted that there was a significant increase in reported cases of anaphylaxis with iohexol, with 24 cases occurring in 2024 compared to an annual average of nine cases over the previous three years. Based on the sales data, it was estimated that the annual number of patients exposed to iohexol in 2024 did not increase compared to the annual numbers from 2021 to 2023. These 24 cases (15 males, 9 females) involved patients aged between 18 to 83 years. Iohexol was reported as the only suspected drug in all except three cases. The co-suspected drugs were iopromide and chlorhexidine with isopropyl alcohol in the first case, ceftriaxone in the second case and ceftriaxone and

tranexamic acid in the third case. Eleven cases had a history of drug allergies or allergic conditions.

Based on HSA's investigations, there was no indication of manufacturing changes or quality issues which could have contributed to the increase. Globally, the estimated reporting rate of anaphylaxis with iohexol had also remained relatively stable and was within the frequency specified in the Omnipaque™ PI.[2] Since anaphylaxis is an idiosyncratic and unpredictable reaction, fluctuations in the number of cases over the years are expected. Other possible reasons affecting yearly figures include variations in spontaneous AE reporting rates due to over/under-reporting.

Severe cutaneous adverse reactions (SCARs) with modafinil and armodafinil

Modafinil and armodafinil (the R-enantiomer of racemic modafinil) are non-amphetamine central nervous system stimulants with wakefulness-promoting properties.[3] Both modafinil and armodafinil are not registered in Singapore, although they are available in some countries as prescription medicines indicated for narcolepsy, sleep work shift disorder and obstructive sleep apnoea. In Singapore, doctors can apply to HSA to import these medicines for patients with specific medical conditions, such as narcolepsy, through HSA's Special Access Route. These medicines should be used under strict medical supervision.

From January 2024 to March 2025, HSA received nine reports of severe cutaneous adverse reactions (SCARs) associated with use of modafinil and armodafinil. This brought the total number of modafinil/armodafinil-SCAR cases in the AE database to 12. The cases involved nine males and three females, aged between 18 and 57 years old. Nine experienced Stevens-Johnson Syndrome (SJS), while three suffered toxic epidermal necrolysis (TEN). All individuals were hospitalised. These drugs were not prescribed by a doctor. Where reported, the patients had obtained the products from street peddlers in Geylang or from friends and had taken these products to improve alertness or boost energy.

SCARs including SJS and TEN associated with modafinil have been reported during post-market surveillance, and case reports have also been published.[4-7] Most of these cases occurred within two months of therapy initiation. Rare cases have been reported three months after initiation of therapy.[6] Although the incidence of SJS/TEN with modafinil/armodafinil is unclear, based on the number of cases received locally, the reporting rate of SJS/TEN with modafinil has likely exceeded the background incidence rate of one to two cases per million-person years for SJS/TEN. Additionally, modafinil and armodafinil carry a potential risk of dependency and abuse due to their stimulant effects on the brain. In clinical trials, modafinil has produced euphoric and psychoactive effects, altering thinking, mood, feelings, and perception like other central nervous system stimulants.[3] Other AEs associated with modafinil and armodafinil include headache, hypertension, nausea, nervousness, and anxiety.

HSA has issued a press release to alert the public to these cases.[1] Healthcare professionals are encouraged to report any suspected AEs with modafinil or armodafinil to the Vigilance and Compliance Branch of HSA.

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4. J Clin Sleep Med 2018; 14(5): 885–7
5. SN Compr Clin Med 2021; 3: 2673–6
6. Clin Exp Dermatol 2018; 43(2): 191–2
7. Micromedex® (electronic version). Merative, Ann Arbor, Michigan, USA. Available at: https://www.micromedexsolutions.com/ Accessed on 3 March 2025

AE Case in Focus: Test Yourself

A 78-year-old female with a history of type 2 diabetes mellitus (DM) complicated by diabetic macular oedema was started on aflibercept, a monthly intravitreal anti-vascular endothelial growth factor (anti-VEGF). She was also taking gliclazide for type 2 DM, amlodipine, valsartan and spironolactone for hypertension and heart failure with preserved ejection fraction, as well as donepezil for Alzheimer's disease.

Five months after initiation of intravitreal aflibercept, she developed renal impairment with a rise in serum creatinine from a baseline of 70 umol/L to 240 umol/L. Her creatinine continued to worsen gradually to 560 umol/L in the next four months. At the ninth month, her urinalysis showed zero red blood cells, while her urine protein-creatinine ratio was high at 3.19 mg/mg. An ultrasound of the kidneys, ureters and bladder showed increased parenchymal echogenicity of both kidneys and no obstructive lesions (Figure 1). No renal biopsy was done.

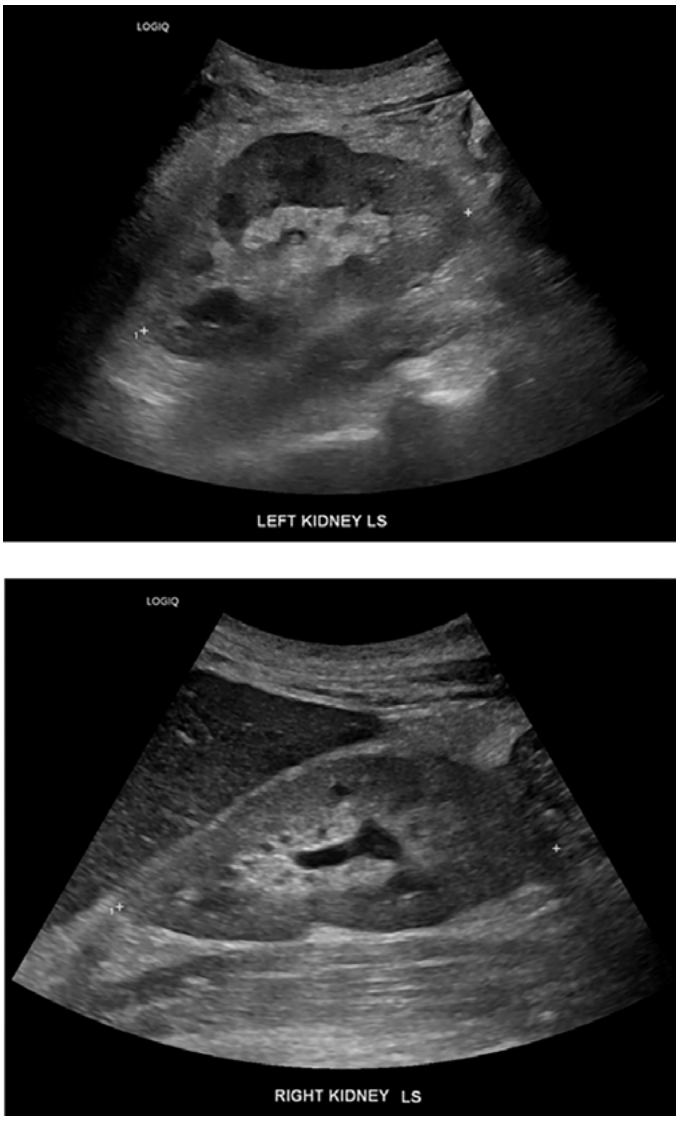

Figure 1. Ultrasound of the kidneys

Question: What could have caused the renal impairment in this patient?

HSA would like to thank Dr. Jeggrey Kam, Associate Consultant from Department of General Medicine at Khoo Teck Puat Hospital for contributing this article.

Answers can be found on page 8

Answer to AE Case in Focus: Test Yourself

The treating physician's assessment was that intravitreal aflibercept could have contributed to this patient's renal impairment. She developed renal impairment with significant proteinuria after receiving more than five months of intravitreal aflibercept. After aflibercept was stopped, there was improvement in renal function, but it did not return to the baseline. Other differential diagnoses were considered, such as lupus nephritis as she had positive anti-dsDNA. However, her complement proteins C3 and C4 levels were not low, and the urinalysis did not show active urine sediment which is to be expected with lupus nephritis. There were also no other features of systemic lupus erythematosus. Another differential diagnosis was hypertensive renal disease. However, the temporal sequence of poorly controlled hypertension and worsening renal function after the initiation of aflibercept, coupled with improvement in renal function after aflibercept was stopped, fits the narrative of aflibercept-induced nephropathy.

Anti-VEGF treatments and nephrotoxicity

Anti-VEGF treatments are mainly used in oncological and ophthalmological diseases. Ophthalmological conditions that can be treated with anti-VEGF agents include diabetic macular oedema, retinal vein occlusion, and neovascular age-related macular degeneration. In these conditions, the anti-VEGF agent is administered intravitreally. Locally approved anti-VEGF agents for ophthalmological indications include ranibizumab, aflibercept, and faricimab. Pharmacokinetic studies have shown that intravitreal administration of anti-VEGF agents can result in significant systemic absorption of the drug, leading to suppression of intravascular VEGF levels.[1]

VEGF serves an important role in maintaining normal kidney function where it is essential for glomerular filtration barrier integrity and regulates blood flow through renal capillaries. Its action on glomerular endothelial cells helps prevent proteinuria and maintains the selective permeability of the glomerulus which is crucial for filtration.[2] Suppression of systemic VEGF level by anti-VEGF agents may lead to renal impairment due to a disruption of the normal VEGF signalling pathways.

There have been overseas case reports of worsening proteinuria, decreased renal function, glomerular diseases and hypertension following the initiation of intravitreal VEGF blockade.[1,3,4] The renal conditions that can result from use of these agents include minimal change disease, focal segmental glomerulosclerosis and renal thrombotic microangiopathy.

Local situation

As at 31 March 2025, apart from the above case, HSA has received two reports of intravitreal anti-VEGF agents suspected to be associated with renal adverse events. The first case was reported in a local study which reviewed 2,225 patients receiving intravitreal injections over an 8-year period.[5] An 85-year-old patient with a history of hypertension, chronic kidney disease and goitre received five doses of intravitreal ranibizumab for wet age-related macular degeneration. The patient subsequently developed renal failure. In the second case, a 73-year-old female developed nephrotic syndrome after receiving three doses of intravitreal aflibercept. The outcome for this case was not reported. There was insufficient information in both cases to ascribe causality to anti-VEGF agents.

HSA's advisory

Healthcare professionals may consider the above information in their management of patients receiving intravitreal anti-VEGF agents and are encouraged to report any adverse events associated with the use of anti-VEGF agents to the Vigilance and Compliance Branch.

References

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3. *Intern Med 2020; 59(23): 3051-4*
4. *Kidney Int Rep 2019; 4(10): 1508-12*
5. *Int Ophthalmol 2017; 37: 325-32*

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