ISSN: 0219 - 2152 May 2022 Vol.24 No.1

ADVERSE DRUG REACTION NEWS

HSA Health Sciences Authority

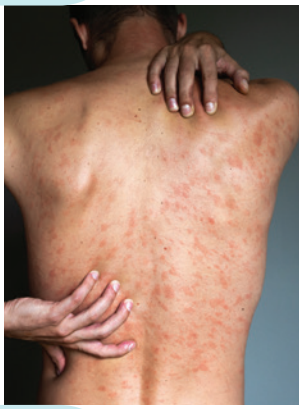
Health Product Safety Information Summary

Scan / click the QR code to read the full issue online

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

AE Case in Focus 1: Test Yourself

What could have caused the rash? Pg 3



This is a case of a 91-year-old male who was started on apalutamide 240mg once a day for his newly diagnosed metastatic castration-sensitive prostate cancer (mCSPC). His past medical history included chronic ischemic heart disease, stage 3 chronic kidney disease, Type 2 diabetes mellitus, hyperlipidaemia and hypertension. He also took various types of medications for his chronic medical conditions. At his first month follow-up consultation, he complained of increased lethargy when he started apalutamide. His prostate specific antigen (PSA) level dropped from 0.36 ug/L to 0.11 ug/L. As the lethargy was bearable, the patient agreed to continue with apalutamide. On Day 61 of his apalutamide treatment, he was admitted to the hospital for extensive rashes on his back since Day 59. The rash started on his back and spread to the anterior chest wall, bilateral inguinal regions and thigh. The rashes were non-tender, non-pruritic, blanchable and maculopapular in nature. The Body Surface Area (BSA) covered was about 15%. There was also mucositis on his inner buccal mucosa. There were no cellulitic change nor necrolysis seen based on Nikolsky's sign (negative). His skin biopsy showed predominantly mild superficial perivascular inflammation and there was only mild dermal mucin of uncertain significance detected.

AE Case in Focus 2: Test Yourself

What could have caused the patient's lethargy? Pg 3

This is a case of an 85-year-old male who was diagnosed with prostate cancer in 2019. He failed abiraterone and started enzalutamide for the treatment of metastatic castration-resistant prostate cancer. His past medical history includes deep vein thrombosis (malignancy-related) and iron deficiency anaemia. He was also taking rivaroxaban and iron supplement. Prior to starting enzalutamide, possible drug interaction with rivaroxaban was noted and his rivaroxaban dose was increased after discussion with the haematologist. His anti-Xa level (rivaroxaban) was measured one month later, while taking the concurrent medications and the levels were found to be appropriate. Three months later, the patient complained of lethargy. There was no shortness of breath, no lower limb swelling and no signs of bleeding.

HSA, Singapore the first national regulatory authority awarded the highest recognition by WHO

We are pleased to share with our healthcare professionals that the Health Sciences Authority (HSA) is the first National Regulatory Authority (NRA) and Singapore is the first World Health Organization (WHO) member state to achieve Maturity Level (ML) 4 for its advanced medicines regulatory system. This achievement came after a rigorous and comprehensive assessment by a team of 19 international assessors and WHO officials using the WHO's Global Benchmarking Tool (GBT) [1] in late 2021.

Enhancing confidence and trust

The ML 4 status identifies HSA as a NRA that is operating at an advanced level of performance and continuous improvement. It confirms the high standards, quality, and rigour of HSA's regulatory work on medicines. This external validation by WHO will enhance our public's confidence and trust in HSA as an innovative and effective medicines regulatory authority working to protect and advance public health and safety. HSA will continue to sustain our culture of operational excellence and continuous improvement and continue our strong collaboration with WHO in regulatory systems strengthening.

Read more about HSA's ML 4 achievement:
WHO Press Announcement
HSA Press Release

[1] WHO's GBT covers over 250 indicators across 8 core regulatory functions that cover the entire regulatory lifecycle of medicines from clinical trials, marketing authorization, post-market safety monitoring, audit and licensing of manufacturers and dealers, and laboratory testing of medicines.

Dear Healthcare Professional Letters on safety concerns

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 2022.

AMOXICILLIN AND RISK OF ASEPTIC MENINGITIS

Key Points

- Very rare cases of aseptic meningitis associated with the use of amoxicillin-containing products have been published in literature
- As this adverse event (AE) can be managed with drug discontinuation, prompt recognition and early diagnosis of amoxicillin-induced aseptic meningitis could prevent aggressive diagnostic procedures and prolonged treatments, as well as the possibility of recurrent episodes related to subsequent use of amoxicillin
- The package inserts (PIs) for amoxicillin-containing products are being updated to state aseptic meningitis as an adverse reaction
- Healthcare professionals are advised to consider the possibility of this AE in patients on amoxicillin-containing products who present with aseptic meningitis after the exclusion of other infectious or disease-related causes

Amoxicillin is a narrow-spectrum beta-lactam antibiotic registered in Singapore since 1998 for the treatment of commonly occurring bacterial infections such as respiratory tract, genitourinary and skin and soft tissue infections. It is available as a single ingredient or in combination with clavulanate, a beta-lactamase inhibitor.

About aseptic meningitis

Aseptic meningitis is a condition where the linings of the brain and spinal cord become inflamed without an infectious cause. Drugs such as non-steroidal anti-inflammatory drugs (NSAIDs), intravenous immunoglobulin and antimicrobials, including amoxicillin, have been identified as potential causes of aseptic meningitis.[1] Other causes include neoplasia, autoimmune, or auto-inflammatory systemic diseases (e.g. systemic lupus erythematosus, rheumatoid arthritis) and iatrogenic etiologies such as complications of a lumbar puncture or intrathecal drug adverse effects. The pathogenesis of drug-induced aseptic meningitis remains unclear but an idiosyncratic delayed-type hypersensitivity reaction has been proposed.[2]

Amoxicillin-induced aseptic meningitis

Very rare cases of aseptic meningitis associated with the use of amoxicillin-containing products have been published in literature.[2-5] Patients typically presented with fever and headache which developed a few hours to seven days after amoxicillin exposure. Photophobia, nuchal rigidity, lethargy, myalgia and general malaise were also present in some cases. Notably, most cases demonstrated positive rechallenge, with two to three episodes of amoxicillin-induced aseptic meningitis. Typical cerebrospinal fluid (CSF) findings consisted of pleocytosis (lymphocytic or neutrophilic), which in some cases were accompanied by elevated protein and usually normal glucose levels (unlike low CSF glucose in bacterial meningitis). CSF cultures were consistently negative.

The diagnosis of amoxicillin-induced aseptic meningitis is usually based on a temporal relationship between drug intake and symptom onset, CSF pleocytosis, negative microbiological tests, and rapid resolution, usually within a few days, after drug discontinuation. As it is a diagnosis of exclusion, a thorough drug history can help support a diagnosis of amoxicillin-associated aseptic meningitis after infectious and disease-related (mainly neoplasms and autoimmune disorders) causes of aseptic meningitis have been ruled out.

Health Canada's review

In 2021, Health Canada reviewed the potential risk of aseptic meningitis in patients treated with amoxicillin-containing products and concluded that there might be a link between amoxicillin-containing products and the risk of aseptic meningitis.[6] Their review took into consideration domestic and international cases of aseptic meningitis associated with amoxicillin use as well as a study of international cases reported to the World Health Organisation (WHO) database, which supported a link between the risk of aseptic meningitis and the use of amoxicillin.

Local situation

To date, HSA has received one report of aseptic meningitis that was possibly associated with the use of amoxicillin/ clavulanic acid.

Currently, aseptic meningitis is a documented AE in the PIs of some amoxicillin-containing products. HSA is working with the product registrants of the remaining products to harmonise this safety information across the local PIs of all amoxicillin-containing products.

HSA's advisory

Amoxicillin-associated aseptic meningitis is a very rare but reversible AE that can be managed with drug discontinuation. As such, prompt recognition of this AE could prevent aggressive diagnostic procedures and prolonged treatments, as well as the possibility of recurrent episodes related to subsequent amoxicillin use. Healthcare professionals are advised to consider the possibility of this AE in patients prescribed amoxicillin-containing products who present with aseptic meningitis after the exclusion of other infectious or disease-related causes.

References

1. *Fundamental & Clinical Pharmacology 2018;32: 252–260*
2. *J Pharm Technol. 2021;37(3):165-166.*
3. *Eur J Case Rep Intern Med. 2020;7(6):001543*
4. *Pharmacoepidemiol Drug Saf. 2019;28(3):389-395*
5. *J Investig Allergol Clin Immunol 2019; 29(3): 239-250*
6. *https://hpr-rps.hres.ca/reg-content/summary-safety-review-detail.php?lang=en&linkID=SSR00276*

AE CASE IN FOCUS 1: TEST YOURSELF

A 91-year-old male was started on apalutamide 240mg once a day for his newly diagnosed metastatic castration-sensitive prostate cancer (mCSPC). His past medical history included chronic ischemic heart disease, stage 3 chronic kidney disease, Type 2 diabetes mellitus, hyperlipidaemia and hypertension. He also took amlodipine, aspirin, atenolol, atorvastatin, enalapril, glipizide, omeprazole, mecobalamin and calcium supplements.

At his first month follow-up consultation, he denied experiencing any rashes, haematuria, urinary urgency or pain. However, he complained of increased lethargy when he started apalutamide. His prostate specific antigen (PSA) level dropped from 0.36 ug/L to 0.11 ug/L. As the lethargy was bearable, the patient agreed to continue with apalutamide.

On Day 61 of his apalutamide treatment, he was admitted to the hospital under the care of a dermatologist. He reported having extensive rashes on his back since Day 59. The rash started on his back and spread to the anterior chest wall, bilateral inguinal regions and thigh. The rashes were non-tender, non-pruritic, blanchable and maculopapular in nature. His face and limbs were not involved. The Body Surface Area (BSA) covered was about 15%. There was also mucositis on his inner buccal mucosa. There were no cellulitic change nor necrolysis seen based on Nikolsky's sign (negative). His skin biopsy showed predominantly mild superficial perivascular inflammation and there was only mild dermal mucin of uncertain significance detected.

Question: What could have caused the rash?

AE CASE IN FOCUS 2: TEST YOURSELF

An 85-year-old male was diagnosed with prostate cancer in 2019. He failed abiraterone and started on enzalutamide for the treatment of metastatic castration-resistant prostate cancer. His past medical history includes deep vein thrombosis (malignancy-related) and iron deficiency anaemia. He was also taking rivaroxaban and iron supplement. Prior to starting enzalutamide, possible drug interaction with rivaroxaban was noted and his rivaroxaban dose was increased after discussion with the haematologist. His anti-Xa level (rivaroxaban) was measured one month later, while taking the concurrent medications and the levels were found to be appropriate. Three months later, the patient complained of lethargy. There was no shortness of breath, no lower limb swelling and no signs of bleeding.

Question: What could have caused the patient's lethargy?

HSA would like to thank Dr Cassandra Chang Wee Ting, Principal Clinical Pharmacist, Singapore General Hospital (SGH) and Dr Kenneth Chen, Consultant, Urology Department, SGH for contributing this article.

Answers can be found on page 8

ANALYSIS OF ADVERSE EVENT (AE) REPORTS FOR YEAR 2021

Key Points

- In 2021, HSA received a total of 21,206 valid adverse event (AE) reports
- For vaccine AEs (excluding COVID-19 vaccines) in children aged 12 years and below, the most commonly reported ones were seizures (febrile and afebrile) with measles, mumps and rubella (MMR), MMR and varicella, varicella, 5-in-1*, pneumococcal conjugate and influenza vaccines. The most commonly reported AEs in adults were allergic reactions such as rash, shortness of breath, angioedema, and injection site reactions with seasonal influenza, hepatitis B, pneumococcal, tetanus, human papillomavirus (HPV) and MMR vaccines
- There were 95 AEs reported with complementary health products (CHP) in 2021. These included three reports of aconitine poisoning with aconite-containing products.

**5-in-1 refers to Diphtheria, Pertussis, Tetanus, inactivated Polio and Haemophilus influenzae Type B vaccine*

This review analyses the AE reports received by HSA in 2021. The scope of this review includes pharmaceuticals [i.e. chemical drugs, biologics, vaccines and cell, tissue and gene therapy products (CTGTP)], CHP and cosmetic products, and highlights reporting patterns which may be of interest.

COVID-19 vaccine AE reports are not included in this review and are discussed separately in the article 'Analysis of COVID-19 vaccine adverse events reports' on page 5.

Report analysis for 2021

(a) Volume of reports

In 2021, HSA received a total of 21,206 valid+ reports which is close to the average annual volume of 23,510 reports received for the past 10 years (i.e. 2011 to 2020).

+ Reports exclude 15,035 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 they could not be assessed for causality.

(b) Sources and types of reports

Majority of the reports were associated with pharmaceuticals (99.5%), which included chemical drugs (96.19%), biologics (1.79%), vaccines (1.5%) and CTGTP (0.02%). The AE reports associated with CHP comprised 0.49%, which included Chinese Proprietary Medicines (CPM), health supplements and traditional medicines. The remaining reports were associated with cosmetic products (0.01%).

Similar to past years, most of the AE reports were from the public sector i.e. public hospitals (53.9%), polyclinics (29.1%) and public specialist clinics (3.9%). The remaining reports were from General Practitioner clinics (9.5%), product registrants (2.6%), as well as private hospitals and specialist clinics (1.0%). Doctors (90.4%) contributed the highest number of reports, followed by pharmacists (5.2%). Reports from dentists, nurses and research coordinators have also been received.

(c) Demographics

Majority of the patients in the AE reports were Chinese (41.5%), followed by Malays (7.8%) and Indians (5.2%). The rest were Caucasians (0.2%), Eurasians (0.2%) and patients whose ethnicity were unreported (45.1%). There were more AE reports received for females (61.7%) than males (37.6%). The age of the patients in the AE reports received ranged from 0 to 111 years old. The highest number of reports comprised elderly patients in the age group of 60 to 69 years old (16.5%) followed by patients in the age group of 50 to 59 years old (15.8%).

AE reports associated with drugs, biologics and CTGTP

The top 20 products suspected of causing AEs were from the following pharmacotherapeutic groups: nonsteroidal anti-inflammatory agents (NSAIDs) (23.0%), antibiotics (16.5%), analgesics (9.9%), drugs for cardiovascular system (CVS) (4.3%), contrast media (2.6%) and gastrointestinal agents (2.5%) (Figure 1). It is worth noting that these figures do not take into consideration the products' utilisation rates and therefore do not inform on their relative safety profiles.

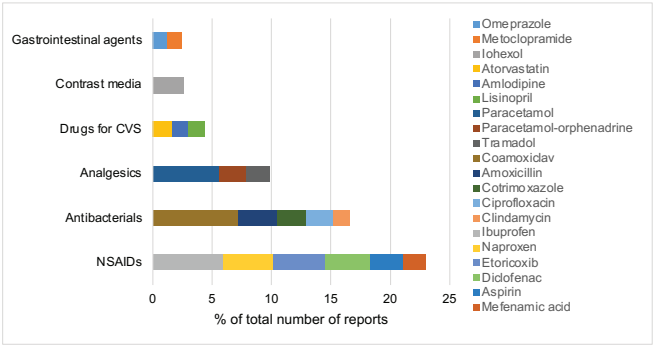


Figure 1. Top 20 products (by active ingredients) suspected of causing AEs

A large proportion of AEs reported were associated with skin reactions (58.9%), followed by those affecting the body as a whole (e.g. fever, anaphylaxis) (20.9%) and respiratory system disorders (7.1%), with most being non-serious reactions (e.g. rash, periorbital oedema, nausea and vomiting). Selected serious AEs and their suspected products are summarised in Table 1.

Vaccine adverse event reports

HSA received 306 vaccine adverse event (VAE) reports in 2021, excluding those associated with COVID-19 vaccines. Of these, 190 (62.0%) reports involved adults and 86 (28.1%) reports involved children and adolescents below 18 years old. Age was not reported for the remaining (9.9%) reports. Most of the reports in children aged 12 years and below were from the active surveillance site at KK Women's and Children's Hospital (n=48), which HSA partners to screen paediatric hospital admissions for AEs post-vaccination.

Similar to past years, the most commonly reported AEs in children aged 12 years and below were seizures (febrile and afebrile) with measles, mumps and rubella (MMR), MMR and varicella, varicella, 5-in-1*, pneumococcal conjugate and influenza vaccines. Other commonly reported AEs in this age group included lymphadenopathy, rashes, thrombocytopenia, Kawasaki disease and injection site reactions associated with various types of vaccines. Vaccine-specific AEs received were vaccine-acquired infections with MMR vaccines and lymphadenitis with Bacillus Calmette-Guerin (BCG) vaccines. AEs in adolescents above 12 years old include fever, headache and dizziness with meningococcal vaccines and isolated reports of rash with human papillomavirus (HPV) vaccine as well as seizure with influenza vaccine.

The most commonly reported AEs in adults were allergic reactions such as rash, shortness of breath, angioedema, and injection site reactions with seasonal influenza, hepatitis B, pneumococcal, tetanus, HPV and MMR vaccines. Other reports received included cellulitis with pneumococcal vaccines and vaccine-acquired infections with varicella zoster vaccines. There were also isolated reports of encephalopathy with influenza vaccine and post-vaccination syndrome (manifestations of extrapyramidal symptoms, encephalopathy and other inflammatory disorders) with co-suspects of Diphtheria, Pertussis and Tetanus (DTP), influenza and varicella vaccines.

Our review of the VAE reports in 2021 did not identify any new safety concerns. Overall, the VAEs received in 2021 were within the expected AE frequencies listed in the vaccine package inserts or in literature.

Complementary health products AE reports

There were 95 AE reports involving CHPs, of which 57 (60%) implicated products classified as health supplements. Majority of these were associated with glucosamine-containing products (n=42, 73.7%), describing mostly hypersensitivity reactions (rash and angioedema). There was an isolated report of QT prolongation with 21st Century Women's Metabolism Increaser, which resolved upon discontinuation of the product.

Table 1. Drugs, biologics and CTGTPs suspected of causing serious AEs

Description	WHO preferred terms	Suspected active ingredient(s) (number in bracket denotes the number of times the pharmaceutical has been implicated in 2021#)	Top 10 suspected active ingredient(s) from 2017- 2021 (number in bracket denotes the cumulative number of times the pharmaceutical has been implicated from 2017 to 2021^)
Skin disorders	Stevens Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN)	Allopurinol (8), Amoxicillin (4), Carbamazepine (2), Celecoxib (2), Coamoxiclav (3), Cotrimoxazole (5), Cyclophosphamide (2), Doxycycline (2), Erythromycin (2), Etoricoxib (2), Levofloxacin (2), Nivolumab (2), Omeprazole (3), Piperacillin-Tazobactam (5)	Allopurinol (37), Amoxicillin (11), Carbamazepine (12), Coamoxiclav (23), Cotrimoxazole (27), Etoricoxib (23), Lamotrigine (9), Omeprazole (24), Phenytoin (11), Piperacillin-Tazobactam (22)
Body as a whole	Anaphylactic Reaction	Amoxicillin (13), Aspirin (16), Atracurium (10), Benzylpenicillin (7), Cefazolin (14), Ceftriaxone (6), Celecoxib (8), Chlorhexidine (7), Ciprofloxacin (9), Coamoxiclav (21), Codeine (6), Cotrimoxazole (6), Diclofenac (21), Etoricoxib (7), Fentanyl (5), Ibuprofen (21), Iohexol (9), Lidocaine (8), Mefenamic acid (10), Morphine (4), Naproxen (24), Omeprazole (12), Paracetamol (20), Piperacillin-Tazobactam (11), Tramadol (4)	Amoxicillin (46), Aspirin (53), Cefazolin (54), Ceftriaxone (44), Ciprofloxacin (41), Coamoxiclav (103), Diclofenac (96), Ibuprofen (88), Naproxen (75), Paracetamol (74)
Central nervous system disorders	Convulsions, Convulsions Grand Mal, Encephalopathy, Meningoencephalitis, Neuroleptic Malignant Syndrome, Neurologic Disorder NOS (not otherwise specified)	Atezolizumab (2), Bevacizumab (2), Cefepime (4), Kymriah (tiasagenlecleucel) (4), Olanzapine (2), Tramadol (2)	Atezolizumab (4), Cefepime (10), Ertapenem (15), Haloperidol (11), Ketamine (4), Kymriah (tiasagenlecleucel) (4), Metoclopramide (10), Olanzapine (6), Quetiapine (4), Tramadol (5)
Renal disorders	Azotaemia, Creatinine Clearance Decreased, Renal Tubular Disorder/ Necrosis, Renal Failure Acute/Chronic, Glomerulonephritis, Nephritis Interstitial, Renal Function Abnormal, Toxic Nephropathy, Nephrosis	Acyclovir (2), Cefazolin (2), Ciprofloxacin (15), Coamoxiclav (4), Diclofenac (4), Enalapril (3), Etoricoxib (6), Hydrochlorothiazide (3), Ibuprofen (2), Lisinopril (3), Losartan (7), Pembrolizumab (6), Telmisartan (3), Vancomycin (2), Zoledronic acid (3)	Ciprofloxacin (57), Cotrimoxazole (15), Diclofenac (22), Enalapril (24), Etoricoxib (26), Hydrochlorothiazide (19), Ibuprofen (21), Lisinopril (23), Losartan (41), Pembrolizumab (12)
Hepatic disorders	Jaundice, Hepatitis, Hepatitis Cholestatic, Hepatic Failure, Hepatocellular Damage, Liver Injury, Coma Hepatic	Allopurinol (3), Atorvastatin (9), Carbimazole (2), Coamoxiclav (9), Cotrimoxazole (3), Dapsone (2), Isoniazid (2), Methotrexate (2), Pyrazinamide (3), Rifampicin (2), Simvastatin (3), Sulfasalazine (3), Telmisartan (2)	Atorvastatin (52), Azathioprine (15), Carbimazole (9), Coamoxiclav (39), Cotrimoxazole (11), Cyclophosphamide (8), Isoniazid (9), Methotrexate (9), Prednisolone (9), Rituximab (10)

 # More than one suspected product may be implicated in a single AE report. Only active ingredients implicated more than once are listed here
^ Based on onset date of the AE

The remaining reports were related to products classified as CPM and/or complementary medicines. These included three AE reports associated with aconite-containing herbs, describing symptoms of aconitine toxicity such as tachycardia, ventricular arrhythmia and paraesthesia. An article on aconitine toxicity has been published in our previous issue in October 2021.[1] An isolated report of raised liver enzymes was received with Hemohim (a product with claims for immune support). Seven reports described AEs of endocrine disorders such as hyperthyroidism, adrenal insufficiency and Cushing's syndrome. These reports led to the detection of three adulterated products ('Traditional Herbs Preparation XPE', 'X-Gout' and 'dcr Natural Herbs Honey Enzyme') by HSA. Press releases have been issued to alert the public of these products and to advise them to exercise caution when buying products online or from unverifiable origins.

Conclusion

Our healthcare professionals' continued vigilance in the reporting of AEs has been invaluable to HSA in the monitoring and timely detection of potential safety signals with health products.

References

1. HSA ADR News Bulletin 2021 October (Volume 23 Number 2)

ANALYSIS OF COVID-19 VACCINE ADVERSE EVENT REPORTS

Key Points

- As of 28 February 2022, a total of 16,394 COVID-19 vaccine AE reports have been reported to HSA for 13,511,751 doses of mRNA vaccines administered
- The most commonly reported AEs with mRNA vaccines were consistent with those typically observed following vaccination and from clinical trials. The incidences of AEs and serious AEs have remained stable at 0.12% and 0.007% of doses administered respectively, since April 2021
- Rare reports of anaphylaxis, myocarditis and pericarditis have been reported with mRNA vaccines. The local incidences for anaphylaxis and myocarditis/pericarditis have remained stable at 0.67 per 100,000 doses administered and 1.10 per 100,000 doses administered respectively
- Very rare cases of cerebral venous thrombosis (CVT) have been reported with the mRNA COVID-19 vaccines, both overseas and locally. The incidence of CVT with mRNA vaccines remains very rare i.e. about 1 additional case of CVT per million doses
- Three hundred and twelve AEs (0.08% of doses administered) including 24 serious AEs (0.006% of doses administered) were reported following the administration of 392,122 doses of Sinovac-CoronaVac COVID-19 vaccine
- Forty-three AEs (0.04% of doses administered) including seven serious AEs (0.007% of doses administered) were reported with Sinopharm COVID-19 vaccine after 100,449 doses were administered
- Based on the local AE reports received as of 28 February 2022, most of the AEs were largely expected with vaccination and reflect what has been reported globally. HSA's current assessment is that the overall benefits of the Pfizer-BioNTech/Comirnaty, Moderna/Spikevax and Sinovac-CoronaVac COVID-19 vaccines continue to outweigh the known risks when used in a pandemic

This review is an analysis of the COVID-19 vaccine AE reports received by HSA from healthcare professionals since the roll-out of the vaccination programme on 30 December 2020 up till 28 February 2022.

The COVID-19 vaccines that are authorised by HSA for use in Singapore under the Pandemic Special Access Route (PSAR)* are listed in Table 1. HSA has also approved the import of Sinopharm inactivated COVID-19 vaccine for use under the Special Access Route× in July 2021.

** https://www.hsa.gov.sg/hsa-psar*
× https://www.hsa.gov.sg/therapeutic-products/register/special-access-routes/SAR-covid19

Table 1. COVID-19 vaccines authorised in Singapore

Vaccines	Type of vaccine	Authorisation date
Pfizer-BioNTech / Comirnaty+	mRNA	14 December 2020
Moderna/Spikevax	mRNA	3 February 2021
Sinovac-CoronaVac	Inactivated	23 October 2021
Nuvaxovid^	Recombinant adjuvanted spike protein	3 February 2022

+The interim authorisation for Pfizer-BioNTech/Comirnaty COVID-19 vaccine was transitioned to product registration on 10 December 2021
^ Nuvaxovid had not yet been supplied to Singapore as of 28 February 2022

Safety monitoring and review of AE reports of COVID-19 vaccines

Most of the reports (80%) were submitted by healthcare professionals from the vaccination centres, public hospitals and polyclinics. The rest were contributed by General Practitioner clinics, specialist clinics, private hospitals and vaccine companies.

As the COVID-19 vaccines were rolled out to large segments of our population, HSA enhanced our post-market monitoring framework to ensure that serious safety concerns with the vaccines are detected promptly. HSA encouraged active reporting of serious AEs by healthcare professionals and utilised data analytics that leverages the nation's deidentified electronic medical records to monitor and assess safety signals.

With the widespread use of the COVID-19 vaccines, including the elderly and patients with underlying medical conditions, serious events and medical conditions may occur around the same time as when the vaccines were given. Serious AEs are assessed in terms of their strength of association with the use of the vaccines, taking into consideration the temporal relationship of the events, clinical information and laboratory tests, patients' demographics and medical histories such as underlying or undiagnosed disease or the natural progression of an underlying disease as well as the use of any concomitant medication. HSA appointed expert panels comprising clinicians from neurology, immunology, cardiology, haematology and nephrology to adjudicate serious AEs and provide advice on the assessment of safety signals.

HSA assesses serious AEs in the context of background disease incidence rates to identify any statistically significant increase in incidence of the AE following vaccination that may signal potential safety concerns. HSA also reviews the company's safety reports, international safety reports and literature and works closely with overseas regulatory agencies and international organisations. In addition, HSA considers the biological plausibility of the AEs, the totality of evidence and data from the above sources before drawing conclusions on any increased risk of an AE associated with the vaccines.

Overview of AE reports associated with mRNA vaccines

Pfizer-BioNTech/Comirnaty Vaccine
Moderna/Spikevax Vaccine

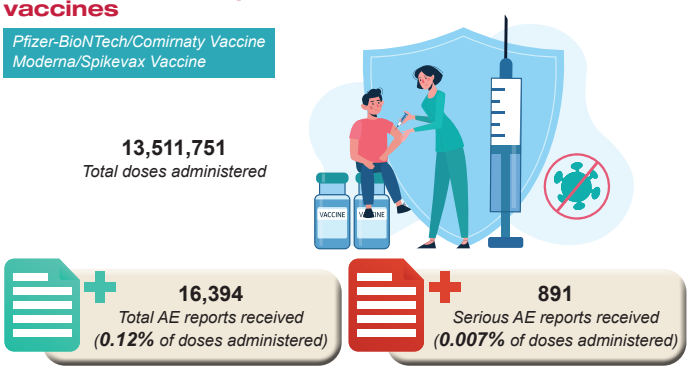


Figure 1. Key statistics for Pfizer/Comirnaty vaccine and Moderna/SpikeVax vaccine (as of 28 February 2022)

As of 28 February 2022, HSA received 16,394 AE reports (0.12% of doses administered) associated with the use of Pfizer-BioNTech/Comirnaty and Moderna/Spikevax COVID-19 vaccines. Eight hundred and ninety-one reports were assessed as serious. These comprised 0.007% of doses administered (Figure 1). The reporting rate of serious AEs has remained stable (between 0.004% to 0.007%) throughout the analysis period since April 2021. In the reports which had included information on outcome, many of the AEs had resolved or were resolving at the time of reporting. Refer to Table 2 for the breakdown of vaccination data and number of AE reports by vaccine brand.

The most commonly reported AEs were allergic reactions (such as rash, pruritus, urticaria and angioedema), dizziness, dyspnoea, chest pain, palpitations, fever and injection site reactions such as pain and inflammation.

The median age of those who had experienced AEs was 42 years (range: 5 to 100 years), with 79% of the AEs reported in individuals below 60 years old. In cases which were assessed as serious, the median age was 43 years. Generally, younger individuals were more likely to experience AEs with the vaccines due to their stronger immune responses. Sixty-three percent of the AE reports were reported in females.

The most frequently reported serious AEs were anaphylaxis (91 reports) and other severe allergic reactions (55 reports). Other serious AEs include:

- immunological – lymphadenopathy, systemic lupus erythematosus and other autoimmune conditions;
- cardiovascular – chest pain, hypotension or hypertension, irregular heartbeat, tachycardia, cardiomyopathy, myocarditis and pericarditis;
- neurological – cerebral venous thrombosis, migraine, neuropathy radiculopathy, hypoaesthesia or paraesthesia, encephalitis, syncope, seizures, Bell's palsy and other cranial nerve palsies;
- haematological – thrombocytopenia;
- thromboembolic – pulmonary embolism and deep vein thrombosis
- musculoskeletal – arthritis including rheumatoid arthritis, myalgia, myositis and rhabdomyolysis;
- dermatological – acute generalised exanthematous pustulosis, eczema flare, psoriasis and bullous pemphigoid;
- renal – nephrotic syndrome and glomerulonephritis;
- ear – tinnitus and sensorineural hearing loss;
- respiratory – exacerbation of underlying asthma and dyspnoea;
- other serious AEs such as abnormal liver function test, appendicitis, hyperthyroidism, vasculitis, menstrual disorders, and infections including herpes zoster.

These serious AEs are closely monitored by HSA, taking into consideration background disease incidence rates and patients' underlying medical conditions to assess the causality of the vaccine with the events.

Table 2. Breakdown of vaccination data and number of AE reports reported by healthcare professionals for mRNA vaccines (as of 28 February 2022)

	Pfizer-BioNTech/ Comirnaty	Moderna/ Spikevax	Total
Total number of doses administered[α]	10,469,306	3,042,445	13,511,751
Number of AE reports	13,433 (0.13% of doses administered)	2,961 (0.10% of doses administered)	16,394 (0.12% of doses administered)
Number of serious[μ] AE reports	728 (0.007% of doses administered)	163 (0.005% of doses administered)	891 (0.007% of doses administered)

[α] The primary vaccination regimens for Pfizer-BioNTech/Comirnaty and Moderna/Spikevax COVID-19 vaccines comprise two doses.

[μ] An AE is classified as serious when the event resulted in hospitalisation/extended stay in hospital, resulted in a significant reduction in functioning level/disability, resulted in a life-threatening illness (e.g. anaphylaxis) or death, resulted in birth defects or is a medically important event.

Overview of AE reports associated with inactivated vaccines

Sinovac-CoronaVac Vaccine
Sinopharm Vaccine

As of 28 February 2022, HSA received 312 AE reports (0.08% of doses administered) following the administration of 392,122 doses of Sinovac-CoronaVac vaccine and 43 suspected AE reports (0.04% of doses administered) following the administration of 100,449 doses of Sinopharm vaccine (Table 3).

Table 3. Overview of number of doses administered and number of AE reports submitted by healthcare professionals for inactivated COVID-19 vaccines (as of 28 February 2022)

	Sinovac-CoronaVac	Sinopharm
Total number of doses administered	392,122	100,449
Number of AE reports	312 (0.08% of doses administered)	43 (0.04% of doses administered)
Number of serious AE reports	24 (0.006% of doses administered)	7 (0.007% of doses administered)

The median age of those who experienced AEs was 46 years (range: 14 to 94 years), with 74% of the AEs reported in individuals below 60 years old. Seventy percent of the AEs were reported in females.

The commonly reported AEs for inactivated vaccines were similar to the mRNA vaccines. These included rash, urticaria, angioedema, dyspnoea, hypoaesthesia, palpitations and dizziness.

Twenty-four serious AEs were reported (0.006% of doses administered) with the Sinovac-CoronaVac vaccine. There were 13 reports of anaphylaxis. The other 11 serious AE reports include myocarditis, Bell's palsy, thrombosis, pulmonary embolism, non-specific sensory syndrome, neuropathy, muscle spasms, sinus tachycardia, hypertension, hearing loss and serious allergic reactions.

There were seven serious AE reports (0.007% of doses administered) associated with the Sinopharm vaccine, describing thrombocytopenia, syncope with myoclonus of limbs, frequent palpitations, chest pain with posterior vitreous detachment, neuropathy, flare of rheumatoid arthritis and relapse of Grave's disease.

Adverse events of special interest (AESI)

As part of the safety monitoring for vaccines, regulatory authorities including HSA have developed a list of "Adverse Events of Special Interest" (AESI). An AESI is a pre-specified medically significant event that has the potential to be causally associated with a vaccine and needs to be carefully monitored and confirmed by special studies. These AESIs include events such as Bell's palsy, anaphylaxis, Guillain-Barré syndrome, myocarditis and thromboembolic events. More AEs may be added to the list of AESIs as more safety data from the use of COVID-19 vaccines becomes available over time.

To date, the more significant AESIs identified with the COVID-19 vaccines are anaphylaxis, myocarditis or pericarditis and cerebral venous thrombosis. Risk mitigation measures were promptly implemented and communicated to the public via HSA's monthly safety updates on COVID-19 vaccines.[1] These included the recommendation of an observation period post-vaccination to manage the risk of anaphylaxis, and the avoidance of strenuous physical activity after vaccination to reduce the risk of myocarditis.

(a) Anaphylaxis

As of 28 February 2022, 104 local AE reports following COVID-19 vaccination were adjudicated as anaphylaxis by HSA's Expert Panel on Hypersensitivity Reactions based on the Brighton Collaboration Case Definition criteria.[2] Forty-seven patients were admitted into the hospital for clinical observation, 53 were treated in the emergency department and the remaining four patients were seen at primary care or were managed by the vaccination centres. All the patients have since recovered at the time of report.

The incidence rate of anaphylaxis with the mRNA vaccines (Pfizer-BioNTech/Comirnaty and Moderna/Spikevax) is estimated to be 0.67 per 100,000 doses administered, with 73 cases reported with Pfizer-BioNTech/Comirnaty vaccine and 18 with Moderna/SpikeVax vaccine. Three of the cases were reported with booster doses of the mRNA vaccines.

Thirteen cases of anaphylaxis were reported with Sinovac-CoronaVac vaccine, with an incidence rate of 3.32 per 100,000 doses administered. All the 13 cases had occurred in individuals with previous allergic reactions to the mRNA vaccines or other vaccine/drugs. Ten patients had previous allergic reactions to the mRNA vaccines, one had previous allergic reaction to the influenza vaccine and two had past histories of multiple drug allergies.

No anaphylaxis cases were reported with Sinopharm vaccine.

(b) Myocarditis and pericarditis

As of 28 February 2022, HSA received a total of 128 reports of myocarditis and pericarditis associated with the COVID-19 vaccines. The cases were adjudicated by HSA's Cardiology Expert Panel using the US Centers for Disease Control and Prevention (CDC) case definition for myocarditis and/or pericarditis in our reports.[3]

Male patients made up 76.6% of the cases, and the median age was 29 years [Interquartile range (IQR), 19 - 41 years]. The median time-to-onset of symptoms was three days (IQR, 1 - 7 days). Majority of the cases (53.1%) occurred after Dose 2 of the vaccine. Sixty-eight percent of the cases were myocarditis (with or without pericarditis), while the rest of the cases were pericarditis (without myocarditis).

Overall, the incidence of myocarditis/pericarditis following COVID-19 mRNA vaccination remains rare, with a reporting rate of 1.1 per 100,000 doses administered for the primary series and 0.7 per 100,000 for the booster doses. The rates were highest in young males aged 12 to 29 years old following Dose 2 (5.6 per 100,000 doses administered). As for the paediatric group aged 5 to 11 years old, one case of myocarditis has been reported, giving a reporting rate of 0.3 per 100,000 doses administered. COVID-19 infection is also known to be associated with myocarditis. In one study, the extra myocarditis events in the month following vaccination was estimated to be between 1 and 10 per million persons, which is substantially lower than the 40 extra events per million persons observed following COVID-19 infection.[4]

The trends observed locally are consistent with international findings, where myocarditis/pericarditis predominantly occurred within a week after mRNA vaccination and in young males following Dose 2. Majority of the patients were treated symptomatically with paracetamol, NSAIDs, colchicine, or did not require any treatment. In six cases, there were more serious outcomes such as longer-term cardiac effects or reduced cardiac function. Such cases remain very rare and should be balanced against the risks of myocarditis associated with COVID-19 infection.

The potential mechanisms of myocarditis and pericarditis following vaccination are yet to be elucidated, but there are several hypotheses, such as autoantibody generation in susceptible individuals,[5] molecular mimicry between the spike protein of the SARs-CoV-2 and self-antigens,[5,6] or greater adaptive immune responses in certain situations (i.e. younger individuals following Dose 2), leading to greater increases of CD4+ Th17+ cell populations, thereby predisposing these individuals to myocarditis.[7] The reason for male preponderance in myocarditis is also unknown, but it is believed to be driven by differences in the sex hormone as testosterone is thought to play a role as a predisposing factor.[4]

(c) Cerebral venous thrombosis

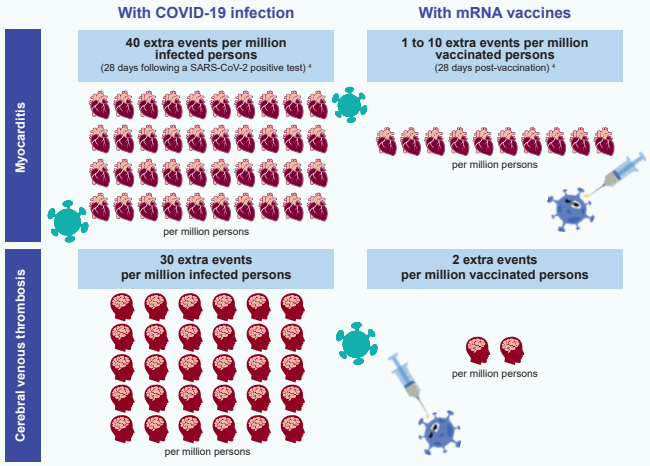
There have been very rare cases of cerebral venous thrombosis (CVT) reported with the Pfizer-BioNTech/Comirnaty and Moderna/Spikevax vaccines, both overseas and locally. The incidence of CVT has stabilised and remains very rare. HSA has received 13 suspected reports of CVT with the mRNA vaccines, out of more than 13 million doses that have been administered. HSA's analysis found a small increase in the incidence of CVT with mRNA vaccines compared to expected baseline incidence rates locally, which translates to about 1 additional case of CVT per million administered doses.

The median time-to-onset of symptoms was 23 days from Dose 1 for 3 cases, eight days from Dose 2 for 9 cases and two days from the booster dose of the mRNA vaccine for the remaining one case. The presenting symptoms of the patients included focal neurological deficits, headaches and seizures.

All the patients were reported to be recovering upon discharge from hospital or undergoing rehabilitation at the time of report.

Risk of myocarditis and CVT with COVID-19 infection versus reporting rates following mRNA vaccination

It is important to note that COVID-19 infection can also lead to myocarditis and CVT. Based on HSA's assessment of the local data and published studies, the incidence of myocarditis[4] and CVT associated with COVID-19 infection is observed to be significantly higher than the AE reporting rates associated with the mRNA vaccines.



Conclusion

Since the roll out of COVID-19 vaccines globally, vaccination has been shown to reduce deaths and severe illness from COVID-19, and to reduce the transmission of COVID-19. Based on the local AE reports received, most of them were those that were largely expected with vaccination and reflect what have been reported globally. HSA's assessment is that the overall benefits of the Pfizer-BioNTech/Comirnaty, Moderna/Spikevax and Sinovac-CoronaVac COVID-19 vaccines in preventing COVID-19 and serious complications associated with COVID-19 outweigh the known AEs when used in a pandemic.

Healthcare professionals are reminded to report all suspected serious AEs associated with COVID-19 vaccines to HSA:

- all fatal and life-threatening events should be reported **within 24 hours** (Note: Fatal events are reportable as Coroner's cases under the Coroners Act)
- all other serious AEs and AESIs are to be reported as soon as possible and within 48 hours

Healthcare professionals are also required to notify the National Immunisation Registry as soon as possible, **within 48 hours**, of all persons who have been vaccinated with the COVID-19 vaccines through the respective IT systems. Please refer to the Dear Healthcare Professional Letter on the monitoring of the safety profile of COVID-19 vaccines issued by HSA on 29 December 2020.[8] Your continued vigilance and support have been invaluable in the detection of potential safety signals and for HSA to take the necessary regulatory actions to safeguard public health.

References

1. https://www.hsa.gov.sg/COVID19-vaccines-safety-updates
2. Vaccine 2007; 25(31): 5675-84
3. MMWR Morb Mortal Wkly Rep 2021; 70(27): 977-982
4. Nat Med 2021; 28: 410-422
5. Circulation 2021; 144: 471-484
6. Circulation 2021; 144: 506-508
7. Clin Pharm Therap 2021; 111(3): 605-613
8. https://www.hsa.gov.sg/announcements/dear-healthcare-professional-letter/monitoring-the-safety-profile-of-covid-19-vaccines

ANSWERS TO AE CASE IN FOCUS 1 AND 2: TEST YOURSELF

In **AE Case in Focus 1**, apalutamide was the most probable cause of the rash in view that it was the only change in medication recently, and the latency period of two months is compatible with what is expected with apalutamide.[1] Clinical trial data also indicates that rash is one of the most common AEs for apalutamide. Apalutamide was then discontinued.

The patient was given lignocaine viscous gel and triamcinolone oral paste for his mucositis and betamethasone 0.1% ointment for his body / limb rash. He was kept under observation in the hospital until Day 67 to monitor for signs of Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN).

On Day 173, during his dermatology follow up, there was a new onset of rash on his bilateral forearm, while the rash on his trunk appeared to be resolving. Mucositis had resolved since his discharge from the hospital. His PSA level rose from 0.09 ug/L to 1.2 ug/L.

Four months later, he was followed up at the urology clinic. His PSA level increased to 4.8 ug/L, and total testosterone was 0.66 nmol/L. He was clinically well. In view of the PSA progression and an uncertain cause of rash, the patient was rechallenged with a reduced dose i.e. half his daily dose (120mg daily) of apalutamide upon agreement by the patient and his family.

After Day 3 to Day 4 of apalutamide rechallenge, he presented to the A&E Department on Day 10 with a recurrence of rash. He had generalised xerotic skin extending from the neck to the chest, back and upper limbs, and extended down to the groin as well. There was no mucosal involvement of glans nor any oral or eye involvement. His rash on the trunk, back, upper arm and shin was different from the rash found over his thigh. He was given oral fexofenadine daily and mometasone ointment to apply on his trunk and limbs.

He returned on Day 30 for his dermatology follow-up and reported that his rashes have generally improved with an occasional skin itch. The patient was subsequently offered alternative treatment agents for his prostate cancer.

In **AE Case in Focus 2**, the patient's lethargy was likely caused by enzalutamide, as shown in a clinical trial where 36% had reported feeling fatigued while taking enzalutamide.[2] A strategy of dose reduction was used and the recommended dose of 160mg was halved to 80mg. Rivaroxaban was also reduced to 10mg in view of the dose reduction of enzalutamide. At follow up reviews, the patient showed that he could tolerate the reduced dosage of enzalutamide well through the improvement of his fatigue.

About Hormonal Therapy for Prostate Cancer

Hormonal therapy is a cornerstone of treatment for prostate cancer. Antiandrogens, or androgen receptor antagonists prevent the binding of male hormones to the receptors and thus block the downstream effects of these hormones in the body. Examples of traditional androgen receptor antagonists used to treat prostate cancer are bicalutamide, flutamide, and nilutamide. Now, there are newer generation hormonal agents for prostate cancer which acts by inhibiting the synthesis of androgens or by blocking the binding of androgens to the target receptor. In the last decade, two anti-androgens, apalutamide and enzalutamide were registered locally for the treatment of metastatic prostate cancer.

Apalutamide is registered for the treatment of non-metastatic castration-resistant prostate cancer (nmCRPC) and metastatic castration-sensitive prostate cancer (mCSPC).

Enzalutamide is registered for the treatment of nmCRPC, mCSPC and metastatic castration-resistant prostate cancer (mCRPC).

1) Rash with apalutamide

Apalutamide-associated rash occurs in 26% of participants in the two major clinical trials. A sub-group analysis suggests that the presentation of rash could be different in the Japanese compared to global population.[1] Limited information is available in the Chinese population.

The presentation of rash may differ in different populations. Prescribers of apalutamide have to monitor patients closely at least for the first three months after initiation of apalutamide. The patient should be informed to stop therapy immediately at the occurrence of rash and to return earlier for review. It is advisable to be well-versed with the management of apalutamide-associated rash and involving a dermatologist should be considered for a multidisciplinary management of the condition, especially for high grade or persistent rashes. Prescribers would also need to consider dose reduction, temporary treatment interruption or treatment discontinuation for patients who present with such rashes. Most of these rashes can be easily managed with steroid creams and antihistamines.

2) Fatigue

Fatigue is common across the disease continuum, with the highest rates among patients with disease progression. A small increase in fatigue was reported by clinical trial patients on enzalutamide vs. patients on placebo for the first 13 to 17 weeks after starting enzalutamide, which stabilized or improved subsequently.[2]

In a clinical trial investigating patients with mCSPC receiving apalutamide (240 mg/day) or placebo, with continuous androgen deprivation therapy, there was no difference in changes of fatigue observed in patients with apalutamide vs. placebo.

Other AEs and potential drug interactions with apalutamide and enzalutamide (Table 1)

The most common AEs reported in clinical trials for apalutamide and enzalutamide were asthenia/fatigue, back pain, hot flush, constipation, arthralgia, decreased appetite, diarrhoea and hypertension.[3] Some of these AEs such as fatigue could result in falls and fractures which are associated with serious outcomes especially in the elderly who are frail and prone to falls. This can affect the patient's quality of life. A rare AE that has been reported in patients receiving enzalutamide is Posterior Reversible Encephalopathy Syndrome (PRES). PRES is a neurological disorder which can present with rapidly evolving symptoms including seizure, headache, lethargy, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension.

Table 1. AEs, monitoring parameters and metabolic pathway for apalutamide and enzalutamide

Drug	Warning, precautions and AEs	Monitoring parameters	Metabolism effects
Apalutamide	Rash, fatigue, hypertension, hypothyroidism, falls and fractures	Thyroid Stimulating Hormone (TSH), T4 levels	Substrate of CYP2C8 (major), CYP3A4 (minor) --- Induces CYP2C19 (++), CYP3A4 (++), CYP2C9 (+), P-gp (+)
Enzalutamide	Seizure, falls and fractures, fatigue, hypertension, PRES	Monitor for signs and symptoms of ischemic heart disease. Optimize management of cardiovascular risk factors (e.g., hypertension, diabetes, or dyslipidaemia)	Substrate of CYP2C8 (major), CYP3A4 (major) --- Induces CYP2C19 (+), CYP2C9 (+), CYP3A4 (++)

Drug interactions

Generally, many of the metastatic prostate cancer patients are in the geriatric age group with multiple comorbidities. Hence it is particularly important to review their concomitant medications. Apalutamide is a major inducer of CYP3A4 which may reduce the plasma levels of CYP3A4 substrate, such as amlodipine, thereby reducing its antihypertensive effects. Hence, monitoring of blood pressure is vital. Other significant drug interactions include rivaroxaban, dabigatran, warfarin, nifedipine and omeprazole.

Enzalutamide is a major inducer of CYP3A4, moderate inducer of 2C9 and 2C19 and may lead to a decrease in drugs as listed above. In addition, enzalutamide is hepatically metabolised primarily by CYP2C8 and CYP3A4, hence it is also contraindicated with concurrent use of CYP3A4 inducers, such as rifampicin and carbamazepine, as this may decrease the bioavailability of enzalutamide.

Role of healthcare professionals in AE monitoring

Healthcare professionals are encouraged to look out for and manage the various AEs associated with hormonal therapies, such as rash and lethargy which may cause serious outcomes that could affect quality of life of patients, and potential drug interactions that may increase the risk of serious AEs from these agents. Healthcare professionals may report any suspected serious AEs to the Vigilance and Compliance Branch of HSA. Your support towards the national AE monitoring programme is invaluable in safeguarding public health.

References

1. *BMC Urol. 2020 Sept 2; 20(1):139*
2. *Prostate Cancer and Prostatic Dis. 2021. doi: 10.1038/s41391-021-00447-9.*
3. *NEJM 2014; 371:424-433*

Please send your enquiries, comments and suggestions to:

Vigilance and Compliance Branch
Health Products Regulation Group
Health Sciences Authority
11 Biopolis Way, #11-01,
Helios, Singapore 138667

Tel : (65) 6866 1111

Website: http://www.hsa.gov.sg
Email : HSA_productsafety@hsa.gov.sg