

# MADRAC *Bulletin*

For healthcare professionals only

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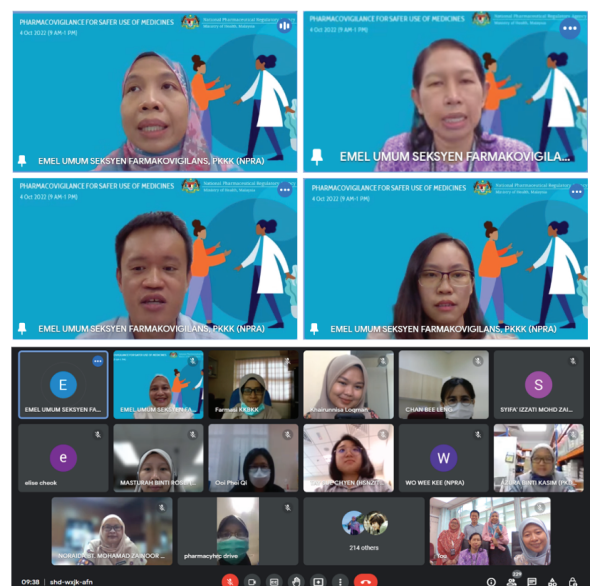
## Features

### Pharmacovigilance Seminar: Pharmacovigilance for Safer Use of Medicines

On 4th October 2022, more than 250 pharmacists virtually participated in the Pharmacovigilance Seminar organised by the National Pharmaceutical Regulatory Agency (NPRA). During the seminar, participants gained knowledge about the Malaysian Pharmacovigilance System, as well as how these four key pharmacovigilance activities — adverse drug reaction (ADR) / adverse event following immunisation (AEFI) monitoring and management, safety signal detection, risk assessment and management, and risk communication — impact patient safety in Malaysia.

The first topic discussed why quality of ADR/AEFI reports matters and how to prepare good-quality reports. The procedures for conducting an AEFI investigation for serious cases and assessing the causality were made clear to the participants. The second topic explained why every ADR/AEFI report counts and how new safety signals are detected from the pool of reports.

In the third session, participants were given an overview of how a safety issue is evaluated and managed with regulatory actions if necessary. Also covered were the scope and workflow for Good Pharmacovigilance Practices (GVP) Inspection. The last topic emphasised the important components of effective risk communication and introduced the mechanisms available in Malaysia for communicating risks and promoting safer use of medicines.



## Articles Based on Case Reports

*This section discusses local individual case safety reports of suspected adverse events recorded in the Malaysian Pharmacovigilance Database (QUEST)<sup>1</sup>. The case reports presented in this section are intended to serve as a reminder of potential adverse events that health providers should be aware of in day-to-day clinical practice, take account of, and report to the NPRA if any relevant events occur. Information contained in these articles is not comprehensive but rather represents a selection of clinically relevant items that warrants dissemination.*

# Risk of Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT) following Vaxzevria (formerly COVID-19 Vaccine AstraZeneca) Vaccination

by Norshazreen Abd Manab

### Case Report 1<sup>1</sup>

A 34-year-old male patient with no known medical illnesses presented with abdominal pain nine (9) days following vaccination with Vaxzevria (formerly COVID-19 Vaccine AstraZeneca). A blood investigation indicated **thrombocytopenia** ( $11 \times 10^9$ ), while a full blood picture indicate no evidence of platelet clumping. An urgent contrast computed tomography (CT) scan revealed features of **portal venous system thrombosis** with hypoperfusion of the spleen and ischaemia of the small bowel loops. The test for **platelet factor 4 (PF4) antibodies** was **positive**.

The patient was initiated on subcutaneous fondaparinux, intravenous immunoglobulin, and intravenous dexamethasone. He later developed gastrointestinal bleeding and hypovolemic shock. Consequently, he was treated with therapeutic plasma exchange, continuous renal replacement therapy, and blood product transfusion. At the time of reporting, the patient was still undergoing treatment.

### Case Report 2<sup>1</sup>

A 31-year-old male patient with no known medical illnesses presented with a severe pulsating headache, a pain score of 8/10, and vomiting. A blood investigation revealed **thrombocytopenia** ( $38 \times 10^9$ ), **raised D-dimer** (1600-3000), and low fibrinogen (1.24 g/L). **Superior sagittal sinus thrombosis** was detected on a CT scan. The test for PF4 antibodies was negative.

Treatment was initiated with subcutaneous fondaparinux, intravenous immunoglobulin, oral prednisolone, oral omeprazole, and oral tramadol. Patient had recovered and is currently well.

### Discussion

COVID-19 vaccines are novel vaccines that have been proven to be highly effective in preventing COVID-19 related illnesses and deaths.<sup>2</sup> In Malaysia, there are currently eight (8) types of COVID-19 vaccines conditionally registered with the Drug Control Authority (DCA).<sup>3</sup> Only five (5) COVID-19 vaccines are in use in Malaysia under the National Immunisation Program for COVID-19 (PICK) since 24<sup>th</sup> February 2021 – namely Comirnaty (Pfizer-BioNTech), CoronaVac (Sinovac), Vaxzevria (AstraZeneca), Convidecia (Cansino), and Covilo (Sinopharm).<sup>4</sup> The National Pharmaceutical Regulatory Agency (NPRA), like all other regulatory authorities around the world, continuously monitors the safety profiles of all COVID-19 vaccines being used in Malaysia.

Very rare cases of thromboembolic events following administration of Vaxzevria (formerly COVID-19 Vaccine AstraZeneca), an adenoviral vector-based vaccine, were first reported in several European countries.<sup>5-6</sup> Following an in-depth review of the available evidence from various sources, including post-marketing reports, quality, clinical, pre-clinical, and literature data, as well as data from product registration holders, the European Medicine Agency's (EMA) had concluded a possible link between the vaccine and the very rare cases of thrombosis accompanied by thrombocytopenia and sometimes bleeding. This serious and potentially fatal adverse event following immunisation (AEFI) has been raised as an adverse event of special interest (AESI). It is termed Thrombosis with Thrombocytopenia Syndrome (TTS), and later more widely known as Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT).<sup>7</sup>

VITT is defined by the combined presence of blood clots and low platelet counts following COVID-19 vaccination, often in uncommon locations (such as the cerebral and splanchnic veins).<sup>3</sup> Thromboses presented in common locations, such as deep vein thrombosis, pulmonary artery/vein thrombosis, cerebral artery thrombosis, and myocardial artery thrombosis, have also been observed.<sup>8</sup> Patients with unusual or persistent symptoms (>72 hours), which include severe headache which do not respond to simple pain killers, visual changes, seizures, abdominal pain, nausea, vomiting, shortness of breath, chest pain, limb swelling/pain/coldness, petechiae or bleeding following COVID-19 vaccination, should be evaluated urgently to rule out VITT.

The pathophysiology and exact mechanisms of VITT remain unclear and require further investigations.<sup>9</sup> However, it has been linked to the presence of anti-platelet factor 4 (anti-PF4) antibodies, similar to autoimmune heparin-induced thrombocytopenia (aHIT). When anti-PF4 binds to platelets, it causes platelet activation and aggregation, thrombosis, platelet consumption, and thrombocytopenia.

Based on currently available evidence, VITT is likely a class effect of the adenoviral vector-based vaccines, including the Vaxzevria and Janssen COVID-19 vaccines (conditionally registered in Malaysia but not

included in PICK).<sup>8,10</sup> According to the review by the United States Food and Drug Administration (US FDA), there is lack of evidence of an association between VITT and mRNA COVID-19 vaccines, such as Pfizer/BioNTech and Moderna vaccines.<sup>11</sup> The majority of cases occurred within 4 to 42 days (most commonly 4–30 days) following vaccination with COVID-19 vaccines, particularly Vaxzevria and the Janssen COVID-19 vaccines, and were more commonly observed in females younger than 50 years old.<sup>8</sup>

As of 31<sup>st</sup> October 2022, the NPRA had received a **total of six (6) reports** of VITT: **five (5) reports** following about 5.7 million doses of the **Vaxzevria vaccine**, included the two (2) cases discussed above, and **one (1)** following about 44.7 million doses of the **Comirnaty vaccine**.<sup>1</sup> The reporting rate of VITT following the Vaxzevria vaccine in Malaysia is **0.88 reports per million doses**, which is considerably lower compared to the reporting rate of 7.7 reports per million doses in the Netherlands.<sup>1,12</sup> The reported time to onset of VITT among local cases was between 7 and 19 days following vaccination.<sup>1</sup> Two (2) of these cases reported cerebral venous sinus thrombosis, while one (1) involved portal vein thrombosis. The remaining VITT cases either lacked imaging evidence or reported a negative platelet factor 4 (PF4) antibodies.

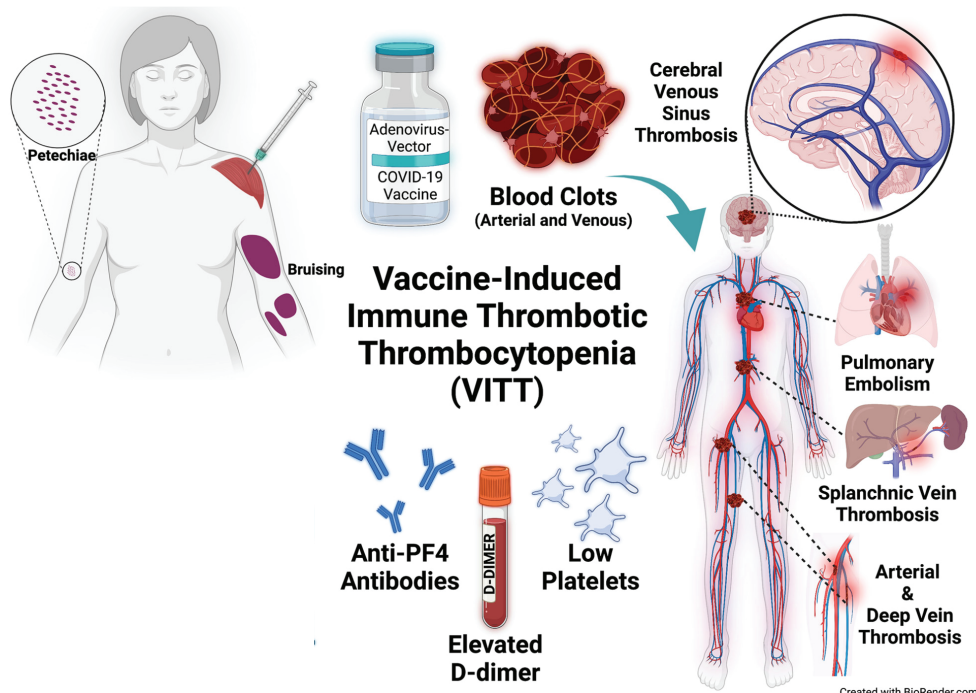


Figure 1: Illustrated summary of vaccine-induced immune thrombotic thrombocytopenia (VITT) associated with COVID-19 adenovirus vector vaccines<sup>13</sup>

The NPRA has previously issued safety updates on the risk of VITT following COVID-19 vaccines. For more information on global scenario, risk population, signs and symptoms, investigations, and treatment, see the [safety alert](#) on the NPRA website as well as the latest Clinical Guidelines on COVID-19 Vaccination in Malaysia.<sup>8,14</sup> The NPRA will continue to monitor the use of the COVID-19 vaccines in Malaysia, to identify any safety signals that may arise, and to ensure the benefits continue to outweigh the risks.

### Advice to Healthcare Professionals

- 1 Reported incidence of VITT is very rare. However, it is crucial to recognise VITT early and promptly initiate urgent medical evaluation and management.
- 2 Be attentive for signs and symptoms of VITT, especially in patients who have recently (4 to 42 days) been administered with any COVID-19 vaccines.
- 3 Educate vaccinees or caregivers about the warning signs and symptoms of VITT and advise them to seek urgent medical attention if these signs and symptoms become severe, unusual, or persist for more than 72 hours.

- 4 Refer a patient of suspected VITT for appropriate investigation and care as early as possible, which is potentially life-saving. Continue to assess patients who present with thrombosis and a normal platelet count post vaccination, as this might be an early stage of VITT.
- 5 Promptly initiate treatment when a patient meets the criteria for a probable or confirmed VITT. When VITT is confirmed, consider a referral to a tertiary care centre with a haematologist. Consider commencing treatment for a possible VITT even if thrombosis has not been confirmed on imaging.
- 6 Be aware that vaccinees who had VITT following the AstraZeneca and Janssen COVID-19 vaccines should not receive this vaccine as the second dose.
- 7 Information on VITT is evolving. Always refer to the most recent Clinical Guidelines on COVID-19 Vaccination in Malaysia for detailed information on the investigations and clinical management of VITT following COVID-19 vaccination.
- 8 Report all suspected adverse events, including VITT following the COVID-19 vaccination, to the NPRA.

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## Articles Based on Case Reports

# Sacubitril/Valsartan: Risk of Psychiatric Events

by Goh Pui Yen

### Case Report 1<sup>1</sup>

A 56-year-old female patient was initiated treatment with sacubitril/valsartan at a dose of 100 mg with an unknown frequency for heart failure. A day after the dose was doubled to 200mg, the patient developed decreased appetite, hypophagia, moderate fatigue, pollakiuria, and mild dyspnoea. Four (4) months later, the patient began to experience lethargy and **mood alteration** with frequent hospital visits and loss of personal independence in daily activities. Over the course of a few months, the patient developed **insomnia** and **psychiatric symptoms**, such as loneliness and helplessness, with general activities affected due to heart failure and dialysis. At the time of reporting, no further information on the outcome of the adverse event was provided.

### Case Report 2<sup>1</sup>

A 72-year-old female patient took sacubitril/valsartan at a dose of 100 mg with an unknown frequency for the treatment of heart failure. After therapy initiation, the patient developed **anxiety** accompanied by dyspnoea but the time-to-onset was not known. The dose of sacubitril/valsartan was then reduced to 50 mg. However, the outcome of the adverse event was not known at the time of reporting.

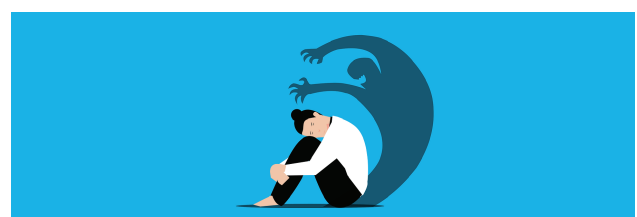
## Discussion

Sacubitril/valsartan belongs to a newer group of drugs termed angiotensin receptor neprilysin inhibitors (ARNIs), which combines a neprilysin inhibitor (sacubitril) and an angiotensin receptor blocker (valsartan).<sup>2-3</sup> In Malaysia, sacubitril/valsartan is indicated to reduce the risk of cardiovascular death and hospitalisation for heart failure in adult patients with chronic heart failure.<sup>4</sup> Sacubitril/valsartan can also be used in combination with other heart failure therapies (e.g., beta blockers, diuretics, and mineralocorticoid antagonists) as appropriate, in place of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB).

The combined inhibition of neprilysin and the renin–angiotensin–aldosterone system (RAAS) by ARNIs, which acts synergistically to prevent cardiac remodelling and support cardiomyocyte survival, provides superior effects over conventional ACE inhibition or ARB inhibition alone.<sup>2-5</sup> These complementary cardiovascular benefits are supported by the enhancement of vasoactive peptides, such as natriuretic peptides, which are degraded by neprilysin.<sup>3-4</sup>

It has been determined that there is a reasonable possibility of a causal association between sacubitril/valsartan and psychiatric events following the European safety review of all available data obtained from literature, spontaneous reports including multiple cases with a close temporal relationship, a positive de-challenge and/or re-challenge and plausible mechanism of action.<sup>6</sup> Psychiatric adverse events that were reported to be associated with sacubitril/valsartan include hallucination, sleep disorder, and paranoia.<sup>6-7</sup>

The exact mechanisms of how sacubitril/valsartan cause these psychiatric events remain unknown.<sup>8</sup> Neprilysin is one of the enzymes involved in the degradation of beta-amyloid proteins, which play a role in the pathogenesis of neurodegenerative diseases. It has been hypothesised that the psychiatric occurrences could be associated with an unintentional increase of beta-amyloid deposition in the brain following the suppression of neprilysin.<sup>8-9</sup> Nevertheless, recent findings from a literature case report indicate that the hypothetical accumulation of beta-amyloid protein appears unlikely, given that the observed psychiatric episodes had an acute onset and resolution.<sup>8</sup>



The time to onset of psychiatric events reported in the literature ranged from two (2) to seven (7) days after starting treatment or escalating the dose.<sup>8,10</sup> It has been reported that these psychiatric events were regarded as serious, resulting in hospitalisation or significant clinical consequences for the patients and their families. However, all patients reported in the literature did not experience a recurrence of psychiatric symptoms after stopping or reducing the dose of sacubitril/valsartan, with some patients confirming full recovery without antipsychotic treatment.

In Malaysia, there are currently three (3) registered products that contain sacubitril/valsartan.<sup>11</sup> To date, NPRA has received 257 adverse drug reaction (ADR) reports with 744 adverse events (AE) suspected to be related to sacubitril/valsartan.<sup>1</sup> The most frequently reported adverse events for sacubitril/valsartan were dyspnoea (73), fatigue (57), and pollakiuria (46).

Following the issuance of a [safety alert](#) by the NPRA in September 2021, the total number of reports involving psychiatric events that the NPRA received increased from four (4) reports to **10 reports to date**.<sup>1,12</sup> Among the **19 psychiatric events** reported were agitation (2), restlessness (2), insomnia (2), difficulty sleeping (1), anxiety (1), aggression (1), mood swings (1), mood altered (1), depressed mood (1), emotional disorder (1), hallucination (1), confusional state (1), disorientation (1), suicidal ideation (1), mental disorder (1), and psychiatric symptom (1), which included the two (2) cases described above.<sup>1</sup>

As of September 2022, a search of the VigiBase, the World Health Organisation (WHO) global pharmacovigilance database<sup>13</sup>, revealed a total of 5,507 (5.9% of all reported events) adverse events belonging to System Organ Class (SOC) Psychiatric Disorder suspected to be associated with sacubitril/valsartan. Among the top reported events under the SOC Psychiatric Disorder were insomnia (21.5%), anxiety (12.8%), confusional state (11.7%), stress (10.9%), and depression (10.5%).

#### \*DISCLAIMER

VigiBase is the WHO global database of reported potential adverse effects of medicinal products, developed and maintained by Uppsala Monitoring Centre (UMC). This information comes from a variety of sources, and the likelihood that the suspected adverse effect is drug-related is not the same in all cases. This information does not represent the opinion of the UMC or the WHO.

## Advice to Healthcare Professionals

- 1 Be aware that psychiatric events such as hallucinations, paranoia and sleep disorders, have been associated with sacubitril/valsartan use.
- 2 Educate patients and caregivers on the possible risk of psychiatric adverse events following sacubitril/valsartan use and to seek medical attention if they experience any psychotic signs and symptoms.
- 3 Consider discontinuation of sacubitril/valsartan treatment if the patient develops any psychiatric events.
- 4 Report all suspected adverse events associated with sacubitril/valsartan-containing products to the NPRA.

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## What's New?

# List of Directives Related to Drug Safety Issues

NPRA reviews and presents drug safety issues at MADRAC meetings to determine the appropriate risk minimisation measures. Regulatory actions are proposed to the Drug Control Authority (DCA), resulting in DCA directives issued to ensure local package inserts and consumer medication leaflets (RiMUP) of all products containing the affected active ingredients are updated with the required safety information. The table below shows the DCA directives that were recently issued, which are available on the NPRA website.

|   | Active Ingredient        | Safety Issue                                                         | Date        | Directive Ref. No.           |
|---|--------------------------|----------------------------------------------------------------------|-------------|------------------------------|
| 1 | Iodinated Contrast Media | Risk of Hypothyroidism (Particularly in Newborns and Young Children) | 07-Oct-2022 | [NPRA.600-1/9/13 (11) Jld.1] |
| 2 | Methadone                | Risk of Hypoglycaemia                                                | 07-Oct-2022 | [NPRA.600-1/9/13 (12) Jld.1] |
| 3 | Piperacillin             | Risk of Haemophagocytic Lymphohistiocytosis (HLH)                    | 07-Oct-2022 | [NPRA.600-1/9/13 (13) Jld.1] |
| 4 | Sertraline               | Risk of Microscopic Colitis                                          | 07-Oct-2022 | [NPRA.600-1/9/13 (14) Jld.1] |
| 5 | Labetalol                | Risk of Nipple Pain and Raynaud's Phenomenon of the Nipple           | 07-Oct-2022 | [NPRA.600-1/9/13 (15) Jld.1] |
| 6 | Donepezil                | Risk of QT Prolongation and Torsade de Pointes                       | 19-Dec-2022 | [NPRA.600-1/9/13 (18) Jld.1] |

## How to report adverse drug reactions?

NPRA encourages all healthcare professionals to report all suspected adverse drug reactions to medicines, including vaccines, over-the-counter medicines, as well as traditional and health supplements.

To report adverse drug reactions:

1. Visit [www.npra.gov.my](http://www.npra.gov.my)
2. Report ADR as healthcare professional.
  - a) Choose [Online Reporting](#) or
  - b) Download the [ADR manual form](#) and submit the completed form via email or post:

[fv@npra.gov.my](mailto:fv@npra.gov.my)



The Pharmacovigilance Section,  
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