MADRAC Bulletin

For healthcare professionals only
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The MADRAC Bulletin is a bi-monthly publication that provides a selection of local safety signals and articles discussing local individual case safety reports (ICSRs) meant to raise awareness among health care professionals. Information contained in this publication is not comprehensive but rather represents a selection of clinically relevant items warranting enhanced dissemination.

The MADRAC Bulletin also features pharmacovigilance-related activities conducted by the National Pharmaceutical Regulatory Agency (NPRA) and contains a list of directives based on safety issues advised by the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) and endorsed by the Drug Control Authority (DCA) as well as safety alerts that have been published on the NPRA website.

To receive each new issue of this bulletin, complete the subscription form available on the NPRA website.

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What's New

We would like to thank the Director General of Health, Malaysia for his permission to publish the case report articles.

Articles Based on Case Reports

This section discusses local individual case safety reports of suspected adverse events recorded in the Malaysian Pharmacovigilance Database (QUEST).[1] The case reports presented in this section are intended to serve as a reminder of potential adverse events that health care 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.

Sodium Valproate: Risk of Acute Pancreatitis

By Nur Ayuni Binti Ahmad

Case Report 1 [1]

A 19-year-old Chinese male patient presented to the hospital with a **pancreatic pseudocyst**. He had been on oral sodium valproate 400 mg twice daily and oral lamotrigine 25 mg once daily for epilepsy for the past seven (7) years. No other underlying medical illnesses were reported. Therapeutic drug monitoring showed that his sodium valproate level was within the therapeutic range (54.7 mcg/mL). Sodium valproate was subsequently withdrawn and substituted with levetiracetam. The outcome of the adverse event was unknown at the time of reporting. In view of the potential presence of confounding factors over an extended period, concomitant drugs, and an unknown dechallenge outcome, the drug-reaction causal relationship between the drug and the observed event in this case was assessed as *C3 possible*.

Case Report 2 [1]

A 16-year-old Malay male patient presented to the hospital with abdominal pain that persisted for a day and was not resolved by medications. He had been taking oral sodium valproate 500 mg thrice daily for epilepsy for 11 years, and no other medical illnesses were known. When an abdominal ultrasound suggested necrotising pancreatitis, the diagnosis of **acute pancreatitis secondary to sodium valproate** was made. Sodium valproate was withdrawn, and the patient was given injection phenytoin thrice daily. At the time of reporting, the patient had not yet recovered from the adverse event. Considering the potential presence of confounding factors over an extended period and an unknown dechallenge outcome, a *C3 possible* drug-event causal relationship was assigned to this case.

Discussion

Sodium valproate is generally indicated for the treatment of neuropsychiatric illnesses, including epilepsy and bipolar disorder.[2-3] There are 10 registered products containing sodium valproate in Malaysia, available in the form of tablets (6), syrups (3), and injection (1).[4]

Acute pancreatitis is commonly presented with a sudden onset of symptoms, such as abdominal pain, abdominal distension, nausea, vomiting, fever, diarrhoea, jaundice, as well as elevated levels of serum amylase and lipase.[5-8] Local or systemic complications, such as pancreatic pseudocysts, fluid accumulation, infections, sepsis, or chronic pancreatitis, may also arise.[6-7]

Sodium valproate-induced acute pancreatitis is characterised as an idiosyncratic complication, which lacks a clear association with the treatment duration, dosage, or serum levels of valproate.[5-7] Its occurrence has been reported within 1 week to 12 years following exposure to sodium valproate.[7] Potential contributory risk factors include the younger age group, severe seizures, severe neurological impairments, combined anticonvulsant therapy, and a prior history of drug sensitivity.[2,6-7]

The precise mechanism underlying sodium valproate causes pancreatitis remains elusive.[8-10] Several studies have proposed a direct toxic effect on pancreatic tissues mediated by free radicals.[6-10] The increased presence of free radicals owing to the decrease of antioxidant enzymes, such as superoxide dismutase, catalase, and glutathione peroxidase, may contribute to enhanced endothelial permeability and lipid peroxidation, leading to tissue damage that induces pancreatitis. Additionally, it has been suggested that the decrease in carnitine levels caused by sodium valproate use plays an important role in pancreatic damage.[7]

Even though acute pancreatitis associated with sodium valproate is a rare occasion, severe and potentially fatal cases may happen.[2,5] Observed patient outcomes vary from full recovery after drug discontinuation to severe acute pancreatitis and death, with the likelihood of fatal outcomes increases with pancreatitis-related hepatic failure.[2,10] Early recognition and prompt management of sodium valproate-associated acute pancreatitis have reported positive outcomes.[7,10]

To date, the NPRA has received 650 local adverse drug reaction (ADR) reports with 1,101 adverse events associated with sodium valproate use.[1] The most commonly involved system organ classes (SOC) were skin and subcutaneous tissue disorders (357), nervous system disorders (140), and investigations (123), with thrombocytopenia (66), pruritus (60), and rash maculo-papular (60) being the most frequently reported adverse events.

At the time of writing, there were **six (6) local cases suspected of sodium valproate-related pancreatitis** involving five (5) male and one (1) female between 3-36 years old, including the two (2) cases described above.[1] The reported adverse events were pancreatitis acute (3), pancreatitis (1), pancreatitis necrotising (1), and pancreatic pseudocyst (1). Of these six (6) cases, only one (1) patient was reported as not yet recovered, while the outcomes of the remaining patients were unknown.

As of January 2023, a search of VigiBase, the World Health Organisation (WHO) database, identified 2,077 cases reporting acute and chronic pancreatitis of all subtypes under the MedDRA High-Level Term (HLT), including pancreatitis (1,317), pancreatitis acute (592), and pancreatitis necrotising (83), suspected to be related to sodium valproate use.[11*]

*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 for Health Care Professionals

1. Remain vigilant about the risk of acute pancreatitis in patients receiving sodium valproate therapy, regardless of therapy duration, especially in those with potential risk factors, as serious and potentially fatal complications may arise if left undetected.
2. Advise patients to seek medical attention as soon as possible if they experience early signs and symptoms of pancreatitis, including sudden abdominal pain, fever, diarrhoea, and vomiting.
3. Promptly perform blood investigations (e.g., serum amylase and lipase) as well as radiology imaging for patients on sodium valproate presenting with clinical features of pancreatitis.
4. In cases where sodium valproate-induced acute pancreatitis is diagnosed, immediately and permanently discontinue sodium valproate use, and consider an alternative treatment.
5. Report any adverse events related to products containing sodium valproate to the NPRA.

References:

1. National Pharmaceutical Regulatory Agency (NPRA). The Malaysia National ADR Database (QUEST) [Internet]. 2023 [cited 2023 Jan 11]. Available from: https://www.npra.gov.my (access restricted)
2. National Pharmaceutical Regulatory Agency (NPRA). The Malaysian Product Registration Database (QUEST). Sodium valproate [Package Insert]. 2023 Jan [cited 2023 Jan 11]. Available from: http://www.npra.gov.my
3. Owens MJ, Nemeroff CB. Pharmacology of valproate [Internet]. Psychopharmacol Bull. 2003;37 Suppl 2:17-24. Available from: https://pubmed.ncbi.nlm.nih.gov/14624230/
4. National Pharmaceutical Regulatory Agency (NPRA). QUEST3+ Product Search [Internet]. 2023 [cited 2023 Jan 11]. Available from: https://www.npra.gov.my
5. Ali MF, Loh KY. Sodium valproate induced necrotising pancreatitis: A case report. Malaysian family physician: the official journal of the Academy of Family Physicians of Malaysia. 2013;8(3):28.
6. Jones MR, Hall OM, Kaye AM, Kaye AD. Drug-induced acute pancreatitis: a review. Ochsner J [Internet] 2015 Spring;15(1):45-51. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4365846/
7. Kaur P, Bhasin D, Singh H, Kundra TS. A Rare Complication of Valproate-Induced Acute Pancreatitis in an Adult Patient with Bipolar Disorder: A Case Report. EMJ Gastroenterol. 2023. Available from: https://doi.org/10.33590/emjgastroenterol/10308417
8. Guevara-Campos J, González-Guevara L, Vacaro-Bolívar I, Rojas JM. Acute pancreatitis associated to the use of valproic acid. Arq Neuropsiquiatr. 2009 Jun;67(2B):513-5. Available from: https://doi.org/10.1590/s0004-282x2009000300028
9. Hamad AE, Fawzi ME. Valproate associated acute pancreatitis [Internet]. Neurosciences (Riyadh). 2000 Jul [cited 2023 Jan 11];5(3):156-8. Available from: https://pubmed.ncbi.nlm.nih.gov/24276803/
10. Jain A, Haque I, Tayal V, Roy V. Valproic acid-induced acute pancreatitis. Indian J Psychiatry. 2019 Jul;61(4):421-422. Available from: https://doi.org/10.4103%2Fpsychiatry.IndianJPsychiatry_383_18
11. Uppsala Monitoring Centre (UMC). The WHO Global ICSR Database (VigiLyze) [Internet]. 2023 [cited 2023 Jan 11]. Available from: https://www.vigilyze.who-umc.org (access restricted).

Risk of Acute Kidney Injury with Dabigatran in Patients with Atrial Fibrillation

By Farah Faridah Binti Jamaludin

Case Report1

A 73-year-old female with a medical history of hypertension, type 2 diabetes mellitus, and dyslipidaemia was started on oral dabigatran 150 mg twice a day for atrial fibrillation during her last discharge. Twelve days later, she presented at the emergency department with complaints of vomiting, poor oral intake, and loss of appetite over the past three (3) days. Upon examination, her renal profile revealed elevated serum creatinine levels. The patient was diagnosed with **acute kidney injury (AKI) secondary to dabigatran**. Following the withdrawal of dabigatran, her serum creatinine level showed a decrease within a week. ***Figure 1*** illustrates the chronology of AKI manifestations in relation to dabigatran use. In light of the potential presence of confounding factors, including comorbidities and concomitant drugs, a C3 possible drug-event causal relationship was assigned to this case.

Discussion

Dabigatran, a direct thrombin inhibitor belonging to direct oral anticoagulants (DOACs), is specifically indicated for treating or preventing thrombosis and embolism in certain medical conditions, including reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (AF).[2-3] Dabigatran undergoes approximately 80% renal elimination and is contraindicated in patients with severe renal impairment (creatinine clearance <30 mL/min).[2,4] In Malaysia, there are currently three (3) registered products that contain dabigatran etexilate, the prodrug of the active ingredient dabigatran, in capsule formulations.[5]

Acute kidney injury (AKI), characterised by an abrupt deterioration of kidney function with a significant surge in serum creatinine, can lead to increased morbidities and mortality.[6-8] Continuous declines in kidney function have been observed in patients with AF receiving anticoagulants, including dabigratran.[9-10] Compared to warfarin, dabigatran was associated with a significantly lower risk of AKI and a slower decline in eGFR.[6,10] However, periodic monitoring and maintenance of adequate renal function are crucial in AF patients receiving dabigatran, as worsening renal function has been linked to increased risks of stroke and bleeding.[10]

Two possible mechanisms underlying dabigatran-induced AKI have been proposed: first, tubular obstruction by red blood cells (RBCs); and second, damage to the renal tubules and interstitium caused by inhibition of protease-activated receptor 1 (PAR-1) from reduced thrombin activities by anticoagulants.[8,11-12] Conditions such as renal vasoconstriction, ischaemia, pro-inflammatory cytokine release, and oxidative stress, collectively contribute to renal damage. A recent single-centre

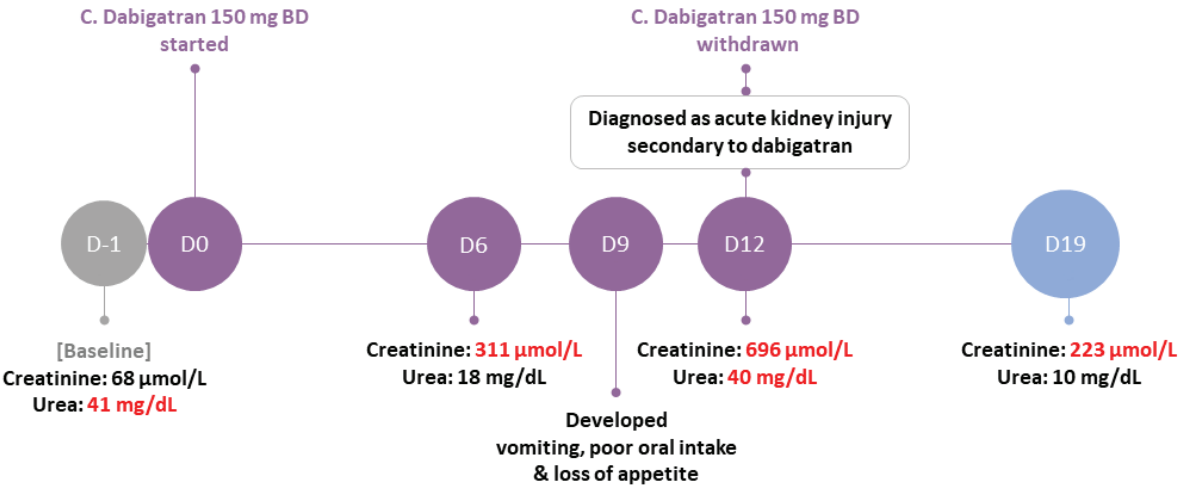

Figure 1: Timeline of clinical manifestations of acute kidney injury event in relation to dabigatran use. D: Day

study reviewing kidney biopsies suggests that, rather than directly affecting the glomerular filtration barrier, excessive anticoagulation with warfarin/DOAC aggravates underlying glomerular diseases and increases glomerular haematuria, which lead to RBC casts formation and acute tubular necrosis.[12]

At the time of writing, the NPRA has received 391 adverse drug reaction (ADR) reports with 694 adverse events suspected to be associated with dabigatran use.[1] The most commonly involved system organ class (SOC) was gastrointestinal disorders (207 events) with upper gastrointestinal haemorrhage (25) being most frequently reported.

Locally, of the 47 events involving SOC Renal and urinary disorders, **AKI (8), acute kidney failure (2), and renal failure (2)** were reported in patients aged 60 years old and above within days to months following dabigatran use.[1] Five (5) of these, including the discussed case, reported underlying AF. At the time of reporting, one (1) case was noted as recovering, three (3) were not recovered, three (3) reported fatal outcomes, and the remaining cases had unknown outcomes. Other reported renal events included haematuria (20) and renal impairment (5). Globally, a search of World Health Organisation (WHO) international ADR database (VigiBase) identified 1,636 reports of AKI and 729 reports of renal failure suspected to be associated with dabigatran use.[13*]

*DISCLAIMER

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Advice for Health Care Professionals

1. Be aware of the risk of acute kidney injury following dabigatran administration in patients with atrial fibrillation.
2. Perform a renal function test prior to and during dabigatran treatment in all patients and especially in the elderly.
3. Consider closer monitoring in patients under certain clinical conditions where a decline in renal function is suspected during dabigatran treatment (e.g., hypovolaemia, dehydration, and concomitant use of certain medicinal products).
4. Advise patients to seek immediate medical attention if they notice any signs and symptoms of acute kidney injury and bleedings, such as reduced urine output, nausea, loss of appetite, itchy skin, pink or brown urine, bruises, or any bleeding events.
5. If a patient develops acute kidney failure, discontinue dabigatran and refer to clinical guidelines for appropriate management and switching to an alternative treatment.
6. Report all suspected adverse reactions related to dabigatran use to the NPRA.

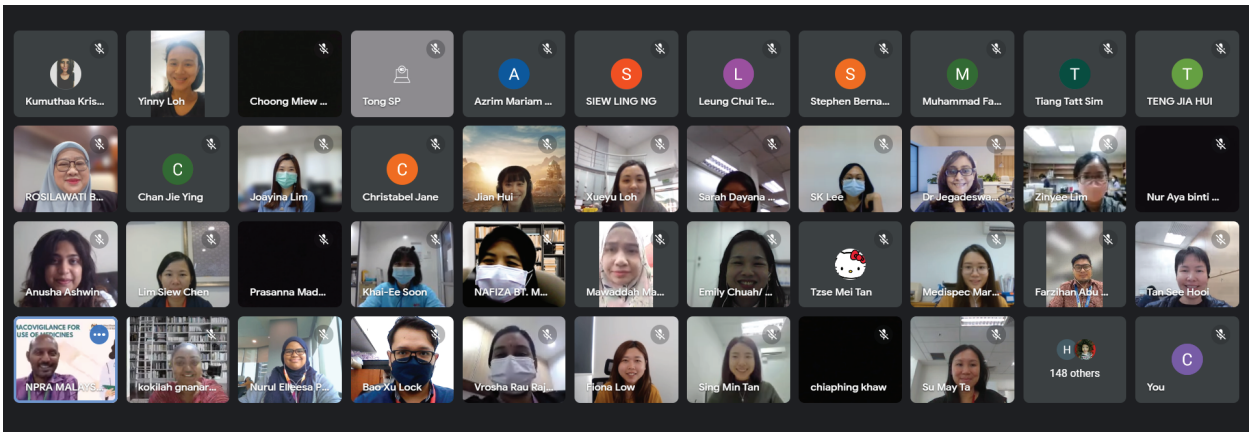
References:

1. National Pharmaceutical Regulatory Agency (NPRA). The Malaysian National ADR Database (QUEST) [Internet]. 2022 [cited 2022 Dec 31]. Available from: https://www.npra.gov.my (access restricted)
2. National Pharmaceutical Regulatory Agency (NPRA). PRADAXA (dabigatran) [Package Insert]. QUEST3+ Product Search. 2020 Sep [cited 2022 Dec 31].Available from: http://www.npra.gov.my.
3. Ministry of Health Malaysia. Clinical Practice Guideline (CPG) for Atrial Fibrillation (AF) 2012. [Internet] [cited 2022 Dec 31]. Available from: https://www.moh.gov.my/moh/resources/Penerbitan/CPG/CARDIOVASCULAR/11.pdf
4. Hijazi Z, Hohnloser SH, Oldgren J, Andersson U, Connolly SJ, Eikelboom JW, Ezekowitz MD, Reilly PA, Siegbahn A, Yusuf S, Wallentin L. Efficacy and safety of dabigatran compared with warfarin in relation to baseline renal function in patients with atrial fibrillation: a RE-LY (Randomized Evaluation of Long-term Anticoagulation Therapy) trial analysis. Circulation. 2014 Mar 4;129(9):961-70. Available from: https://doi.org/10.1161/circulationaha.113.003628
5. National Pharmaceutical Regulatory Agency (NPRA). QUEST3+ Product Search [Internet]. 2022 [cited 2022 Dec 31]. Available from: https://www.npra.gov.my
6. Luo S, Derbas LA, Wen Y, Arif S. Tracy M, Wasserlauf J, Huang HD, Reiser J. Oral anticoagulant and relative risk of acute kidney injury in patients with Atrial Fibrillation: A systematic review and network meta-analysis. American Heart Journal Plus: Cardiology Research and Practice. Available from: https://doi.org/10.1016/j.ahjo.2022.100132
7. Patschan D, Müller GA. Acute kidney injury. J Inj Violence Res. 2015 Jan;7(1):19-26. doi: 10.5249/jivr.v7i1.604. Available from: https://doi.org/10.5249%2Fjivr.v7i1.604
8. Patel S, Hossain MA, Ajam F, Patel M, Nakrani M, Patel J, Alhillan A, Hammoda M, Alrefaee A, Levitt M, Asif A. Dabigatran-Induced Acute Interstitial Nephritis: An Important Complication of Newer Oral Anticoagulation Agents. J Clin Med Res. 2018 Oct;10(10):791-794. Available from: https://doi.org/10.14740%2Fjocmr3569w
9. Böhm M, Ezekowitz MD, Connolly SJ, Eikelboom JW, Hohnloser SH, Reilly PA, Schumacher H, Brueckmann M, Schirmer SH, Kratz MT, Yusuf S, Diener HC, Hijazi Z, Wallentin L. Changes in Renal Function in Patients With Atrial Fibrillation: An Analysis From the RE-LY Trial. J Am Coll Cardiol. 2015 Jun 16;65(23):2481-93. Available from: https://doi.org/10.1016/j.jacc.2015.03.577
10. Yao X, Tangri N, Gersh BJ, Sangaralingham LR, Shah ND, Nath KA, Noseworthy PA . Renal Outcomes in Anticoagulated Patients With Atrial Fibrillation. J Am Coll Cardiol. 2017 Nov, 70 (21) 2621–2632]. Available from: https://doi.org/10.1016/j.jacc.2017.09.1087
11. Ryan M, Ware K, Qamri Z, Satoskar A, Wu H, Nadasdy G, Rovin B, Hebert L, Nadasdy T, Brodsky SV. Warfarin-related nephropathy is the tip of the iceberg: direct thrombin inhibitor dabigatran induces glomerular hemorrhage with acute kidney injury in rats. Nephrol Dial Transplant. 2014 Dec;29(12):2228-34. doi: 10.1093/ndt/gft380. Epub 2013 Sep 5. PMID: 24009280. Available from: https://doi.org/10.1093/ndt/gft380
12. Brodsky SV, Satoskar A, Hemminger J, Rovin B, Hebert L, Ryan MS, Nadasdy T. Anticoagulant-Related Nephropathy in Kidney Biopsy: A Single-Center Report of 41 Cases. Kidney Med. 2019 Mar-Apr;1(2):51-56. Available from: https://doi.org/10.1016/j.xkme.2019.03.002
13. Uppsala Monitoring Centre (UMC). The WHO Global ICSR Database (VigiLyze) [Internet]. 2022 [cited 2022 Dec 31]. Available from: https://www.vigilyze.who-umc.org (access restricted)

Features

Pharmacovigilance Seminar: Pharmacovigilance for Safer Use of Medicines

On 6th April 2023, the National Pharmaceutical Regulatory Agency (NPRA) hosted a virtual Pharmacovigilance Seminar for private-sector pharmacists. This event drew the participation of over 250 pharmacists across Malaysia from a variety of fields, including the pharmaceutical industry, hospitals, community pharmacies, clinics, and academia.



This Pharmacovigilance Seminar aimed to heighten awareness among private-sector pharmacists about the importance of reporting of adverse drug reactions (ADR) and adverse events following immunisation (AEFI), to improve the quality of reports sourced from private sector for enhancing local safety signal detection, and to provide a deeper understanding of how pharmacovigilance activities impact the safety of medicines in Malaysia.

During the seminar, participants gained insights about the Malaysian Pharmacovigilance System and learned about how four principal pharmacovigilance activities—ADR/AEFI monitoring and management, safety signal detection, risk assessment and management, and risk communication—contribute to safer use of medicines in Malaysia.

In the initial session, participants grasped the importance of the quality of ADR/AEFI reports and they were guided on how to construct high-quality reports. The following session enlightened them on how new safety signals are detected from a range of sources, including local ADR/AEFI reports, reference countries, notifications from product registration holders (PRHs), the evaluation of periodic safety documents, and published literature. Subsequently, participants were briefed on the process of safety issue evaluation and the types of regulatory actions necessary for managing the risks. Lastly, the seminar underscored the crucial elements of effective risk communication, and participants gained familiarity with the various channels available for risk communication within Malaysia.

What's New

List of Safety Alerts/Directives Related to Drug Safety Issues

NPRA reviews and presents drug safety issues at meetings of the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) 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 information leaflets (RiMUP) for all products containing the affected active ingredients are updated with the required safety information. The table below shows the safety alerts/DCA directives that were recently issued, which are available on the NPRA website.

	Active Ingredients	Safety Alerts (SA)	SA Date	Directive Ref. No. [Date]
1	Diclofenac Suppositories	Off-Label Use to Treat Fever in Children: Potential Risk of Acute Necrotising Encephalopathy of Childhood (ANEC)	11-Apr-2023	-
2	Azacitidine	Risk of Differentiation Syndrome	19-Apr-2023	NPRA.600-1/9/13 (23) Jld.1 [11-Apr-2023]
3	Comirnaty Vaccine	Risk of Heavy Menstrual Bleeding	02-May-2023	-
4	Griseofulvin	Risk of Severe Cutaneous Adverse Reactions (SCARs)	03-May-2023	NPRA.600-1/9/13 (22) Jld.1 [11-Apr-2023]

How to report adverse events?

NPRA encourages all health care professionals to report all suspected adverse drug reactions (ADR) to medicines, including pharmaceutical products, over-the-counter medicines, traditional medicines, and health supplements, as well as adverse events following immunisation (AEFI) with vaccines.

To report ADR/AEFI:

1. Visit **www.npra.gov.my**
2. Report ADR **as Health Care 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

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