

MADRAC *Bulletin*

For healthcare professionals only

Volume 62 | Issue 05/2026

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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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DISCLAIMER

The MADRAC Bulletin is published by the National Pharmaceutical Regulatory Agency (NPRA), Ministry of Health (MOH), Malaysia. This publication is meant to provide updates on medication safety issues to health care professionals, and not as a substitute for clinical judgement. While reasonable care has been taken to verify the accuracy of the information at the time of publication, the NPRA shall not be held liable for any loss of whatsoever arising from the use or reliance on this publication. The opinions expressed in all articles are the authors' own and do not necessarily reflect the view of NPRA.

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 exhaustive but rather represents a selection of clinically relevant items that warrants dissemination.

Warfarin-induced Calciphylaxis

By Ng Wan Ning

Case Report¹

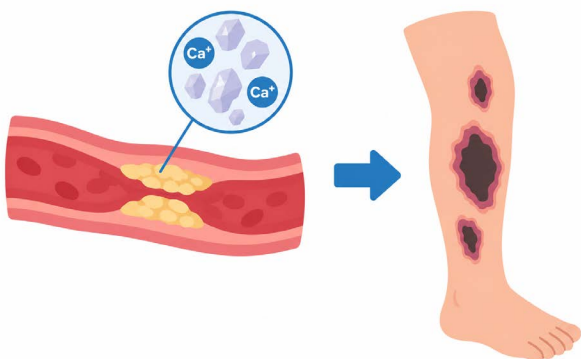
A 48-year-old male had underlying hypertension, dyslipidaemia, end-stage renal disease on regular haemodialysis, as well as perimembranous ventricular septal defect (VSD) associated with pulmonary hypertension. He was prescribed oral warfarin 2 mg once daily for atrial fibrillation, calcium carbonate as a phosphate binder and sildenafil for pulmonary hypertension. Approximately 16 months after starting warfarin therapy, the patient developed severe pain, skin induration, and non-healing ulcers with black crusts over the left lower limb. **Calciphylaxis** was suspected, and the diagnosis was subsequently confirmed by skin biopsy. Laboratory investigations revealed low corrected calcium levels (1.78–2.14 mmol/L), elevated phosphate levels (2.00–3.07 mmol/L), and mildly elevated alkaline phosphatase (ALP) levels (130–215 U/L). Warfarin was discontinued, and the patient was treated with intravenous sodium thiosulfate 25 g three times weekly for calciphylaxis. At the time of reporting, the patient was recovering.

Based on the temporal relationship, presence of underlying medical conditions and concomitant medications, the adverse event was assessed as possibly related to warfarin.

Discussion

Warfarin is an oral anticoagulant of the vitamin K antagonist class that inhibits vitamin K epoxide reductase (VKOR), thereby reducing the synthesis of vitamin K-dependent clotting factors II, VII, IX, and X, as well as anticoagulant proteins C and S.² It is indicated for the prevention and treatment of venous thromboembolism, pulmonary embolism, and thromboembolic complications associated with atrial fibrillation or cardiac valve replacement, as well as to reduce the risk of death, recurrent myocardial infarction and subsequent thromboembolic events such as stroke. In Malaysia, there are currently 11 registered products containing warfarin, all available in tablet form.³

Calciphylaxis is a rare but life-threatening condition characterised by calcium deposition in small blood vessels within the dermal and subcutaneous tissues.^{4,5} This leads to vascular calcification, tissue ischaemia, necrosis and ulceration. Clinically, it presents as painful, well-demarcated purpuric plaques or nodules that rapidly progress to non-healing ulcers covered with black eschar.⁴⁻⁶ These lesions most commonly affect the lower extremities and areas with high adipose tissue such as the abdomen, thighs, buttocks and breasts. The overall prognosis for patients with calciphylaxis is generally poor, with an estimated one-year mortality rate of 60-80%.⁵ The presence of ulcerated lesions is associated with an even higher mortality risk because these lesions are highly susceptible to secondary infections that may progress to sepsis, the leading cause of death among patients with calciphylaxis.⁶



**AI-generated image*

Although calciphylaxis most commonly occurs in patients with end-stage renal disease requiring dialysis (estimated prevalence of 1–4%), warfarin use has been associated with an approximately 10-fold increased risk of developing this condition.⁵ Rare cases have also been reported in patients receiving warfarin with normal renal function.^{2,6} Recognising this risk, the NPRA issued a directive in 2016 [BPFK/PPP/07/25/Jld.1] requiring all local warfarin product information to include calciphylaxis as a documented adverse event and to highlight this risk in the Special Warnings and Precautions for Use section.⁷

The exact pathophysiology of warfarin-induced calciphylaxis is not fully understood, however warfarin may contribute to this condition by inhibiting the activation of matrix gamma-carboxyglutamic acid (Gla) protein, a vitamin K-dependent inhibitor of vascular calcification, thereby promoting vascular mineralisation.^{5,6,8,9} The strongest risk factor for warfarin-induced calciphylaxis is end-stage renal disease, particularly among patients requiring dialysis.^{2,4-6,8} Additional risk factors include female gender, calcium–phosphate imbalance, diabetes, obesity, liver disease, autoimmune or hypercoagulable states, and hypoalbuminaemia. The onset of warfarin-induced calciphylaxis is highly variable.^{5,6,10} While it typically occurs after prolonged duration of continuous therapy, symptoms have been reported to emerge as early as one month after starting warfarin treatment or even within a week of re-initiating therapy.^{5,10} Management of calciphylaxis includes discontinuation of warfarin, correction of calcium–phosphate imbalance, and treatment with intravenous sodium thiosulfate.^{6,9} Supportive care includes wound management, infection prevention, and adequate pain control.⁷

To date, the NPRA has received 799 adverse drug reaction reports with 1496 adverse events associated with warfarin use.¹ The most frequently reported adverse events were pruritus (90 cases), international normalised ratio increased (89), and dizziness (68). As of July 2026, NPRA has received one local report of calciphylaxis, as described above. Globally, based on the World Health Organisation (WHO) database, there were 748 reports of calciphylaxis suspected to be associated with warfarin.^{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

- Be **aware** of the risk of calciphylaxis associated with warfarin, which may develop months to years after treatment initiation.
- **Monitor** patients, particularly those with end-stage renal disease requiring dialysis, for signs and symptoms of calciphylaxis such as painful purplish skin lesions (including plaques, nodules, or blisters).
- **Educate** patients on early symptoms of calciphylaxis and **advise** them to promptly seek medical attention for unexplained painful skin rashes, blisters or non-healing ulcers.
- **Consider** skin biopsy to confirm the diagnosis and to differentiate calciphylaxis from other conditions, including warfarin-induced skin necrosis.
- **Discontinue** warfarin immediately if calciphylaxis is suspected and initiate appropriate management.
- **Report** any adverse drug reactions suspected to be related to warfarin use to NPRA.

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Features

New Infographic!

CPD Points for ADR / AEFI Reporting by Pharmacists



National Pharmaceutical Regulatory Agency
Ministry of Health, Malaysia

EARN CPD POINTS While Improving Patient Safety



Did you know?

Pharmacists in Malaysia may claim Continuing Professional Development (CPD) points for submitting ADR / AEFI* reports which meet NPRA's minimum reporting criteria.

*ADR: Adverse drug reaction / AEFI: Adverse event following immunisation

For Pharmacists



Want to Earn CPD points? Here's How:



Complete patient details

Identification number, age, gender, ethnicity



ADR / AEFI description

Date of reaction, time to onset, dechallenge, rechallenge



Suspected drug details

Active ingredient, brand, dose



Reporter details

Name, email address, designation

How to report ADRs / AEFIs?



Scan here to report online
or

Visit the NPRA Web Portal
for other reporting options:



<https://www.npra.gov.my/index.php/en/health-professionals/reporting-adr.html>

*Every detail counts.
Every report matters!*

CLAIM UNDER CPD
CATEGORY

A4



www.npra.gov.my

Thank you for helping keep medicines safe in Malaysia

Pharmacists play an important role in medicine safety by identifying and reporting suspected ADRs or AEFIs. As an added benefit, pharmacists can also earn Continuing Professional Development (CPD) points for submitting complete reports that meet the mandatory reporting criteria set by NPRA.

Since 2015, the Pharmacy Board of Malaysia has agreed to award **one (1) CPD point under Category A4 for each complete ADR / AEFI report** submitted to the NPRA [Ref: KKM-55/BPF/101/001/01 JLD 29 (20) and KKM.600-16/1/6(57)].

To be eligible, the ADR/AEFI report must contain all the required information specified in the infographic above. For private sector pharmacists, NPRA will assess the submitted report and certify its eligibility for CPD points, while for public sector pharmacists, assessment and verification are conducted at the respective healthcare facility.

So, the next time you encounter a suspected ADR or AEFI, report it—your reports help make medicines safer for everyone.

Features

Get ready for #MedSafetyWeek 2026

Get ready for #MedSafetyWeek 2 - 8 November 2026

#MSW2026: Side effects - don't ignore them, report them!



#MedSafetyWeek is a global campaign spearheaded by the Uppsala Monitoring Centre in Sweden, with the aim of enhancing awareness on the safe use of medicines and reporting side effects.

This year, #MedSafetyWeek 2026 marks the **11th global campaign** and Malaysia's 6th consecutive year of participation. Almost **130 countries** have joined the campaign. Join us!

How you can join



**Follow
on social
media**

Follow Program Perkhidmatan Farmasi and Kenali Ubat Anda, or your healthcare facility's social media account



**Share and
use the
hashtags**



Share the #MedSafetyWeek social media posts and don't forget to include #MedSafetyWeek and #MedSafetyWeekMY



**Organise
an
activity**

Organise a short talk, quiz, information booth or other engaging activity to raise awareness on the importance of reporting side effects



Program Perkhidmatan Farmasi



@kenaliubatanda



@kenaliubatanda

Scan here to visit NPRA's #MedSafetyWeek page to know more or visit the NPRA web portal



<https://www.npra.gov.my/index.php/en/health-professionals/medsafetyweek.html>



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	Vancomycin	Risk of Severe Cutaneous Adverse Drug Reactions (SCARs)	14-Aug-2026	NPRA.600-1/9/13(10) Jld.2 [16-Jun-2026]
2	Itraconazole	Risk of Pseudoaldosteronism	26-Aug-2026	NPRA.600-1/9/13(11) Jld.2 [16-Jun-2026]

How to report adverse events?

NPRA encourages all healthcare 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 [Healthcare Professional](#)
 - a) Choose [ADR / AEFI Google Form](#); or
 - b) Download the [ADR manual form](#) and submit the completed form via email or post:



fv@npra.gov.my



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NPRA Safety Information Mailing List



To join the mailing list:

- a) scan the QR code to complete the [subscription form](#), or
- b) send an email with your details to fv@npra.gov.my



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