

MADRAC *Bulletin*

For healthcare professionals only

Volume 48 | Issue 03/2024

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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.

Highlights

Research@NPRA Using Interpretable Machine Learning to Identify Factors That Influence the Quality of Malaysian Adverse Event Reports

WHY IT MATTERS

- **Completeness** of adverse event (AE) reports is crucial for assessing putative causal relationships!
- As of Feb 2019, 5-year average VigiGrade completeness score :

0.79  **>**  **≈0.44**

0.8 = well-documented

 Contributing factors **unexplored**.

OUR WORK

- Analyses of **132,738 Malaysian reports** in WHO VigiBase (2005-2019)
- **INTERPRETABLE MACHINE LEARNING**
 - Identified **key features** that **predict well-documented reports**
- **TIME-SERIES ANALYSES**
 - Examined **chronological trends & characteristics** of reports;
 - Outlined **key strategies & interventions**;
 - Tracked influence of **interventions of interest**.

WHAT WE FOUND

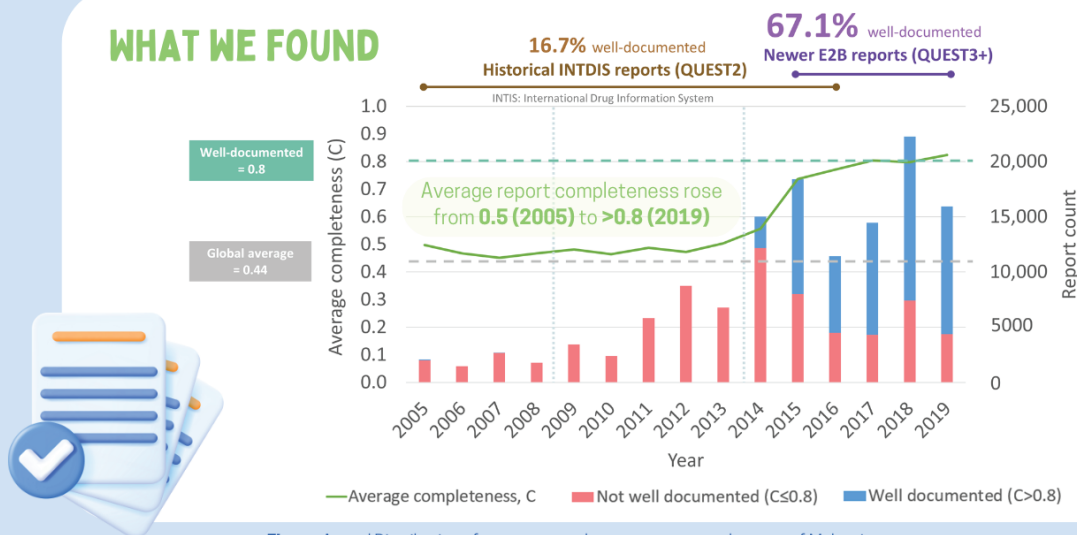


Figure: Annual Distribution of average completeness scores and counts of Malaysian reports by status of being well documented in VigiBase over the study period

FOR WELL-DOCUMENTED REPORTS

POSITIVE FACTORS

- Higher staffing
- Positive drug dechallenge, short reaction onset, short duration of use, shorter dosing interval
- Reports from public specialist hospitals, reports by pharmacists

NEGATIVE FACTORS

- Reports from product registration holders & other health care professionals
- Reactions involving product substitution issues

POSITIVE DRIVERS

- **Multifaceted strategies and interventions comprising policy changes, continuity of education, and human resource development** laid the groundwork for AE reporting in Malaysia.
- **Advancements in technological infrastructure, pharmacovigilance databases, and reporting tools** concurred with increases in both the quantity and quality of AE reports.

STUDY CONCLUSIONS



- Identified **key features** that influence the **completeness of Malaysian AE reports** and unveiled **strategies** to develop **pharmacovigilance capacity** in Malaysia.
- Findings will guide future work in enhancing pharmacovigilance and public health.

A Message from the Authors

Thank You: Immense gratitude to everyone dedicated to reporting adverse events. Your diligent efforts have propelled Malaysia's report quality well above the global average!

Continued Vigilance: Every single report is making a meaningful impact. Let's keep this momentum and continue our joint efforts to safeguard patient safety.



For more information, read the full article published in *JMIR Medical Informatics*.



SCAN HERE

Research Publication **Data-Driven Identification of Factors That Influence the Quality of Adverse Event Reports: 15-Year Interpretable Machine Learning and Time-Series Analyses of VigiBase and QUEST**

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Article 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.

Allopurinol-Induced Photosensitivity Reaction

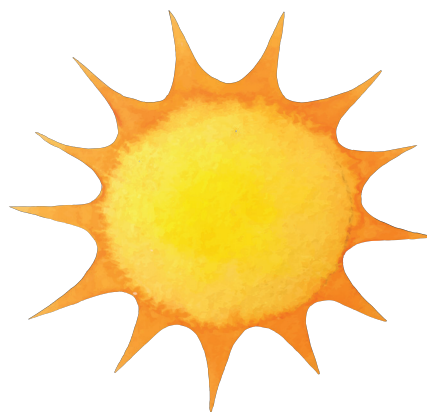
By Jeevenraj Rajagopal

Case Report 1¹

A 63-year-old male with a history of acute coronary syndrome was discharged from hospital with a prescription of allopurinol 150 mg daily for gouty arthritis. Two days following initiation of allopurinol therapy, the patient developed **skin lesions** on both palms, which progressed to **skin desquamation** and spread to other sites with associated **itchiness**. Almost a month later, the patient was referred to the dermatology department due to persistent rash and itchiness. Clinical examination revealed a **maculopapular rash** on the face, neck, and chest, **erythematous macules** with scales over the chest and upper limbs, and **diffuse erythematous** rash over both feet. Allopurinol was discontinued, and subsequent follow-up revealed he recovered from the maculopapular rash, though there was desquamation over the upper limbs. The **final diagnosis by a dermatologist was photodermatitis secondary to allopurinol**. Due to the presence of underlying medical conditions and possible use of concomitant drugs, the adverse event was given a causality *possibly-related* to the allopurinol.

Case Report 2¹

A 42-year-old male with a history of gout was discharged from hospital with a prescription of allopurinol 300 mg daily. Approximately two weeks later, the patient began developing **photosensitive rashes** over his face. Despite the rash, the patient continued taking allopurinol as prescribed. However, his symptoms worsened, leading to his readmission to hospital. Allopurinol was withheld upon readmission, and the rash started to subside. Considering the time-to-onset of reaction and inability to exclude other external factors, the causal relationship of the observed adverse event has been assessed as *possible*.



Discussion

Allopurinol is a xanthine oxidase inhibitor commonly used in the management of chronic gout, uric acid nephropathy, and uric acid stone formation.² It is also indicated for complications arising from hyperuricemia resulting from cancer chemotherapy or radiation therapy. There are currently 11 registered products in Malaysia containing allopurinol as a single ingredient or combination product.³

Allopurinol and its primary metabolite, alloxanthine (oxypurinol), work by inhibiting xanthine oxidase.² This prevents hypoxanthine and xanthine from converting into uric acid. Since hypoxanthine and xanthine are easier to eliminate from the body compared to uric acid, allopurinol helps lower uric acid levels in the blood.

Drug-induced photosensitivity (DIP) results from exposure to ultraviolet (UV) or visible radiation in individuals using systemic or topical drugs with photosensitizing effects.⁴ These reactions may be classified as phototoxic or photoallergic, and may occur hours to days after drug initiation. Please refer to [our previous publication](#) for further details on these reactions.

Diagnostic procedures such as phototesting, photopatch testing, and clinical rechallenge (repeated several months after cessation of the suspected drug) may be conducted to help identify the cause of photosensitivity and confirm the diagnosis.^{5,6}

To date, NPRA has received 3,411 local adverse drug reaction (ADR) reports with 6,020 adverse events suspected to be related to allopurinol.¹ The most commonly reported adverse events are pruritus (833), rash (672), and Stevens-Johnson syndrome (545). There are **13 local reports** linked to allopurinol-induced **photosensitivity** reactions, including the two cases mentioned in this article. These reports involved eight cases of photosensitivity reaction, three cases of photosensitive dermatitis, and two cases of photosensitive rash.

As of May 2024, a search of the World Health Organisation (WHO) global ADR database revealed 186 cases of photosensitivity reaction suspected to be associated with allopurinol.^{7*}

***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 Be vigilant** on the risk of photosensitivity reactions in patients receiving allopurinol, especially those with a history of skin reactions, during treatment initiation, and those on long-term treatment.
- 2 Remind** patients to seek medical assistance immediately if they experience any of the following signs and symptoms: erythema, burning sensation, scaling, pruritus, vesicles, oedema, or hyperpigmentation.
- 3** Severe symptomatic photosensitivity reactions may require **discontinuation** of allopurinol and treatment with a short regimen of either topical or systemic steroid.
- 4** If allopurinol treatment is essential for the patient, **reduce** the dosage or administer the drug in the evening.
- 5 Counsel** patients to practice (i) sun avoidance especially during peak daylight hours, and (ii) sun protection measures, such as applying sunscreens and wearing protective clothing, hats, or sunglasses.
- 6 Report** any adverse events related to products containing allopurinol to the NPRA.

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1. National Pharmaceutical Regulatory Agency (NPRA). The Malaysian National ADR Database (QUEST) [Internet]. 2024 [cited 2024 Mar 6]. Available from: <https://www.npra.gov.my> (access restricted).
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Reminder

ALLOPURINOL

Top suspected drug for **SCARs*** in Malaysia

Useful and effective treatment for gout,
but **counselling** and **close monitoring** is required!

PRESCRIBING

- **Approved indications:**
Gout, renal stones, chemotherapy-induced hyperuricaemia.

Check the product information for complete list of approved indications

- **NOT** for asymptomatic hyperuricaemia

COUNSELLING FOR PATIENTS

- If you experience any of the following symptoms while taking allopurinol, **STOP taking** the medicine immediately and **seek medical attention**.
- Suggest to provide patient information card/educational materials.

Fever



Rash



Symptoms:

Eye irritation



Sore throat



Fatigue



Joint pain



Reporting ADRs[#]

Remember to mention in your ADR report:

- ☒ Name and designation of prescriber who initiated allopurinol treatment
- ☒ Specific indication of allopurinol
- ☒ Renal profile of patient
- ☒ Designation of doctor who made SCARs diagnosis

This information will help NPRA analyse each report and take steps to reduce the risk.

*Notes: *SCAR: Severe cutaneous adverse drug reaction; #ADR: adverse drug reaction*

References: 1. NPRA. MADRAC Bulletin April 2014. Allopurinol: Impact of Risk Minimisation Actions.
https://www.npra.gov.my/images/Publications/Newsletter_MADRAC_Bulletin/Bulletin-MADRAC-Apr-2014.pdf

Any queries?

Please send us an email:
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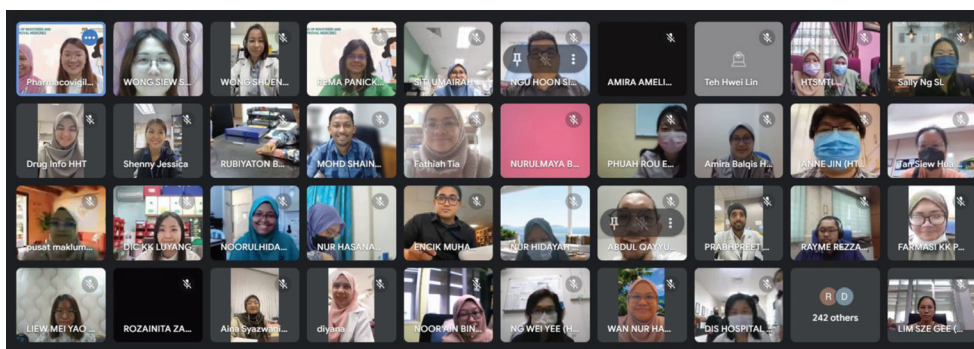
Features

Training

Pharmacovigilance Seminar: Monitoring of Registered and Special Approval Medicines

As part of continuous efforts to enhance pharmacovigilance in Malaysia, NPRA hosted a training seminar on 22 April 2024. This virtual event was attended by more than 350 public-sector pharmacists from across Malaysia.

The seminar aimed to increase understanding on the post-registration monitoring activities of pharmaceutical products, and the impact of these activities on the quality, safety and efficacy of products in Malaysia. Besides providing an introduction to drug safety monitoring in Malaysia, our esteemed speakers delivered sessions on the monitoring of special approval medicines, handling of product complaints, as well as the importance of ADR reporting.



Training

Uganda National Drug Authority Attachment at NPRA

As a WHO Collaborating Centre in the Regulatory Control of Pharmaceuticals, NPRA often conducts training on drug regulatory matters for other countries.

From 6–10 May 2024, a team of five officers from the Uganda National Drug Authority completed an attachment at NPRA. Among the topics covered were NPRA's QUEST 3+ online system, product registration, good manufacturing practices, laboratory processes, and pharmacovigilance.

The NPRA pharmacovigilance team provided attendees with an overview of our pharmacovigilance activities, including ADR monitoring, signal detection, risk assessment, risk management, and communication on the risks or safe use of medicines.



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	Ciprofloxacin, Moxifloxacin, Levofloxacin and Ofloxacin (Fluoroquinolones) for Systemic Use (Oral and Injection)	Risk of Suicidal Behaviours	17-Apr-2024	NPRA.600-1/9/13 (39) Jld.1 [15-Apr-2024]
2	Hydrochlorothiazide	Risk of Acute Respiratory Distress Syndrome (ARDS)	18-Apr-2024	NPRA.600-1/9/13 (43) Jld.1 [15-Apr-2024]
3	Levetiracetam and Clobazam	Risk of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)	29-Apr-2024	-
4	Proton Pump Inhibitors	Risk of Erectile Dysfunction	30-Apr-2024	-
5	Olmesartan	[Updated] Risk of Autoimmune Hepatitis	06-May-2024	NPRA.600-1/9/13 (42) Jld.1 [15-Apr-2024]
6	Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors (Dapagliflozin, Empagliflozin, Canagliflozin)	Interaction with Lithium (for Therapeutic Use) Leading to Decreased Serum Lithium Concentration	28-May-2024	NPRA.600-1/9/13 (40) Jld.1 [15-Apr-2024]
7	Amoxicillin	Risk of Aseptic Meningitis	29-May-2024	-

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:

- Visit www.npra.gov.my
- Report ADR as **Healthcare Professional**
 - Choose **Online Reporting** or
 - 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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