

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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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.

Isotretinoin: Risk of Psychiatric Adverse Effects

By Sabariah binti Pakeer Oothuman

Case Report 1¹

An 18-year-old male patient was initiated on isotretinoin 10mg once a day for the treatment of acne vulgaris following prior therapy on doxycycline, topical adapalene and topical benzoyl peroxide. After one month of isotretinoin therapy, he began to feel **depressed**, was crying and had loss of interest in activities he normally enjoyed. At his follow-up visit with the dermatologist, isotretinoin was discontinued. At the time of reporting, the patient was reported to have recovered from the adverse events. The adverse events were given a causality *possibly* related to isotretinoin.

Discussion

Isotretinoin is an isomer of the active form of vitamin A (13-cis-retinoic acid) and is classified as a retinoid. Isotretinoin is indicated for the treatment of severe forms of acne (nodular acne, or acne at risk of permanent scarring) and acne which has failed to respond to standard therapies such as systemic anti-bacterial and topical therapy.²⁻³ It improves severe acne primarily by suppressing sebaceous-gland activity, reducing sebaceous gland size and exerting dermal anti-inflammatory effects.²⁻³ There are currently eight registered products containing isotretinoin in Malaysia, available in capsule form.⁴

While highly effective, concerns have been raised about a possible association between isotretinoin therapy and **psychiatric adverse effects** including depression, anxiety, mood alteration and psychotic symptoms.²⁻³ Reports of suicidal ideation, suicide attempts and completed suicides have also been documented; although a direct causal relationship has not been established.²

The exact mechanism of isotretinoin-associated psychiatric adverse reactions remains unclear, but several plausible biological pathways have been proposed.^{2,5} Isotretinoin is a lipophilic molecule capable of crossing the blood-brain barrier and it is thought to affect brain regions involved in mood regulation, such as the limbic system.⁵ Studies have shown that isotretinoin reduce hippocampal neurogenesis, alter the function of the thalamus, hypothalamus, and amygdala, decrease metabolic activity in the prefrontal cortex, and affect serotonergic and dopaminergic pathways.^{2,5} Another proposed mechanism is that isotretinoin may interfere with biotin and homocysteine metabolic pathway leading to depressive symptoms.

A meta-analysis by Tan et al. (2024) involving over 1.6 million patients reported that 4.57% of isotretinoin users developed a psychiatric disorder over a one-year.⁶ However, the 1-year absolute risk of suicide attempt and ideation were below 0.5%. A key risk factor for developing psychiatric symptoms while on isotretinoin treatment is a personal or family history of psychiatric disorders.^{2-3,7} Therefore, management of psychiatric adverse events involves careful monitoring for signs of depression or other psychiatric symptoms, particularly in those with a history of depression. If psychiatric symptoms occur, discontinuation of treatment should be considered and referral of patient to appropriate psychiatric treatment.⁷⁻⁸ In some cases, symptoms resolved with dose reduction alone, or with addition of psychotropic medications after stopping isotretinoin.



*AI-generated image

The onset of psychiatric symptoms in patients taking isotretinoin varies but typically occurs within the initial months of therapy. A literature review indicated that depression and suicide commonly appear one to two months after initiation of isotretinoin.⁷ Other case reports, however indicate a wider range of onset time, with symptoms appearing as early as 5 days and up to 5 weeks.⁷⁻⁸

To date, NPRA has received 60 reports with 123 adverse events suspected to be related to isotretinoin. The most commonly reported adverse events were pruritus (6 reports), rash maculo-papular (6) and hyperlipidaemia (5).¹ There are three reported cases of psychiatric disorders involving isotretinoin in Malaysia, including the one discussed in this article. The other two cases involved 18-year-old males who reported depressive moods/symptoms, anxiety and loss of interest after taking isotretinoin. As of September 2025, the World Health Organisation (WHO) international ADR database has reported a total of 18,989 adverse events classified as System Organ Class (SOC) Psychiatric Disorders suspected to be associated with isotretinoin.^{9*} The frequently reported events under SOC Psychiatric Disorder were depression (48.7%), suicidal ideation (15.3%) and mood altered (14.0%). While majority of the cases were reported within the age group of adults (35.2%), a further breakdown within the category saw 32.6% occurring in ages 18-20 years.

This safety issue was highlighted by the United Kingdom Medicines and Healthcare products Regulatory Agency (MHRA) in April 2023. Following recommendations from the Isotretinoin Expert Working Group (IEWG), new safety measures were introduced to strengthen the safe use of isotretinoin, particularly concerning the risks of psychiatric disorders and sexual dysfunction.¹⁰ The NPRA has previously issued a directive [[Ruj. Kami: \(6\) dlm. BPFK/PPP/07/25 Jld. 3](#)] for product registration holders of all oral retinoid products to update the package insert and consumer medication information leaflet (RiMUP) with information regarding the risk of neuropsychiatric disorders. Following that, NPRA has also issued an updated [safety alert](#) on the risk of psychiatric disorder and sexual dysfunction relating to isotretinoin.

***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

- **Conduct** a mental health assessment before starting isotretinoin including screening for history of psychiatric illness.
- **Counsel** patients and their caregivers on the potential risk of psychiatric adverse events such as depression, aggravated depression, anxiety, mood alterations, and psychotic symptoms.
- Encourage family members and friends of patient to be **aware** of the signs of mental health deterioration during treatment.
- **Monitor** mental health status throughout the treatment period, particularly during the initial months.
- If psychiatric symptoms develop, consider **dose reduction, discontinuation of therapy**, and/or a **referral to mental health services**.
- **Report** any adverse events suspected to be related to isotretinoin-containing products to the NPRA.

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Features

Training

Pharmacovigilance Seminar: Enhancing Patient Safety - Pharmacists at the Frontline of Product Monitoring

The NPRA Pharmacovigilance Section conducted an online seminar titled “Enhancing Patient Safety: Pharmacists at the Frontline of Product Monitoring” on 10 September 2025, with participation of over 400 pharmacists from public health facilities nationwide. The sessions underscored the vital role of pharmacists in ensuring medicine safety.

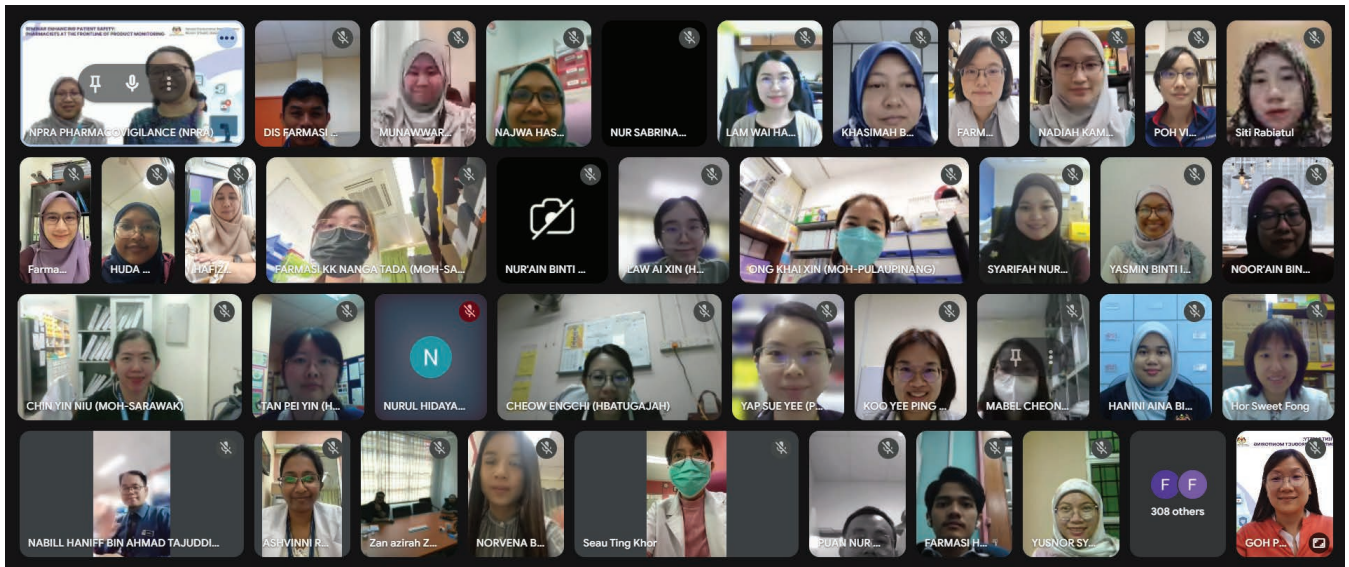
The objectives of this seminar were to:

- enhance understanding of well-documented reports for ADR and AEFI reporting
- strengthen knowledge on reporting product quality complaints
- raise awareness of the importance of high-quality ADR/AEFI reports and their impact on safety assessment and regulatory action
- empower effective medicines risk communication through collaboration between facility-based pharmacists and the NPRA.

The seminar began with speakers from the NPRA Pharmacovigilance Section outlining Malaysia’s pharmacovigilance system and emphasising the importance of complete, well-documented adverse drug reaction (ADR) and adverse event following immunisation (AEFI) reports. They also covered reporting criteria, workflow, regulatory actions and the use of the Vigilyze completeness score by the WHO to indicate quality of reports. This was followed by a session by the NPRA Surveillance and Complaints Section, which shared insights on post-market surveillance, including market sampling, packaging inspection, and handling of product complaints. A subsequent session highlighted how detailed, accurate ADR/ AEFI reports play a crucial role in detecting safety signals and guiding regulatory action, sharing case examples where reports led to label updates, safety alerts and other regulatory decisions. The seminar concluded with a focus on effective risk communication, outlining key principles, stakeholder roles and NPRA resources such as guidelines, bulletins, RiMUPs and safety alerts, alongside initiatives like #MedSafetyWeek to encourage collaboration and wider dissemination of safety information.



Features



Participants gained valuable knowledge and practical insights applicable to their daily work. They were highly engaged throughout the sessions, actively posing questions and seeking clarification, particularly on ADR reporting procedures and requirements. Many also shared observations and challenges from their practice, leading to productive discussions and shared learning among attendees.

NPRA will continue to host further training sessions on pharmacovigilance and other regulatory activities. If there are any specific topics you would like us to cover, please let us know via email at fv@nptra.gov.my.

Get ready for #MedSafetyWeek 2025


#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. The 2025 campaign marks the 10th anniversary of #MedSafetyWeek and Malaysia's fifth consecutive year of participation in this campaign. It will take place from 3 to 9 November 2025, focusing on how we can all help make medicines safer.

Join us! Visit NPRA's [#MedSafetyWeek page](#) to know more about the campaign. Share the #MedSafetyWeek social media posts from Program Perkhidmatan Farmasi. Don't forget to include the hashtags #MedSafetyWeek and #MedSafetyWeekMY



 Program Perkhidmatan Farmasi

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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	Valproate (Sodium Valproate, Valproic Acid)	Potential Risks to Offspring Following Paternal Exposure, and Male Infertility	19-Aug-2025	NPRA.600-1/9/13(62) Jld.1 [18-Aug-2025]
2	Apixaban, Dabigatran, Edoxaban, Rivaroxaban and Warfarin	Risk of Atraumatic Splenic Rupture	22-Aug-2025	-
3	Cyproterone Acetate, Medroxyprogesterone Acetate, Chlormadinone	[Updated] Risk of Meningioma	17-Sep-2025	NPRA.600-1/9/13(61) Jld.1 [18-Aug-2025]
4	Lamotrigine	Erythema Multiforme (EM)	17-Sep-2025	NPRA.600-1/9/13(63) Jld 1 [18-Aug-2025]
5	Hydroxychloroquine	[Updated] 1) Small Increased Risk of Major Congenital Malformations in Children Following in utero Exposure; 2) Risk of Drug-Induced Phospholipidosis; 3) Risk of Aggravation of Myasthenia Gravis	19-Sep-2025	NPRA.600-1/9/13 (64) Jld. 1 [18-Aug-2025]
6	Finasteride and Dutasteride	Risk of Suicidal Thoughts	24-Sep-2025	-


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 **Online Reporting** or
 - b) Download the **ADR manual form** and submit the completed form via email or post:

 fv@npra.gov.my

 Pharmacovigilance Section,
National Pharmaceutical Regulatory Agency (NPRA),
Ministry of Health, Malaysia.
Lot 36, Jalan Prof Diraja Ungku Aziz (Jalan Universiti),
46200 Petaling Jaya, Selangor, Malaysia.

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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