MADRAC Bulletin

For healthcare professionals only
Volume 51 | Issue 06/2024

In this issue

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 healthcare professionals.

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.

Signals

Features

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

Signals

The signals in this Newsletter are based on information derived from reports of suspected adverse events available in the Malaysian Pharmacovigilance Database (QUEST)[1] and the WHO global database of individual case safety reports (VigiBase)[2]. The signal presented below is intended to raise awareness of reported adverse events and stimulate additional reporting from healthcare professionals.*

Amlodipine: A Reminder on the Risk of Gingival Enlargement

Written by Lee Sing Chet; Reviewed by Nora Ashikin Mohd Ali

Background

Amlodipine is a calcium channel blocker indicated as a first-line treatment for hypertension and myocardial ischaemia, used alone or in combination with other antihypertensive or antianginal drugs.[3]

Drug-induced **gingival enlargement** is an overgrowth or increase in size of the gingiva resulting wholly or partially from systemic drug use.[4-5] It is commonly associated with calcium channel blockers, immunosuppressants, and anticonvulsants. We use the term "gingival enlargement" throughout this article. Based on the World Health Organisation (WHO) International Classification of Diseases 11th Revision (ICD-11) code DA0D.1, gingival enlargement includes terms such as ***gingival hyperplasia, gingival hypertrophy***, and ***drug-induced gingival hyperplasia***.[6] The gingival enlargement may result in gum swelling, bleeding, aesthetic issues, and difficulties with chewing or pronunciation. In severe cases, it can lead to tooth mobility and detachment due to alveolar bone absorption.

The proposed mechanisms for **amlodipine-induced gingival enlargement** are categorised into inflammatory and non-inflammatory pathways:[5,7,8]

- *Non-inflammatory pathways* include: (1) inhibition of intracellular calcium ion influx, resulting in reduced cellular folate uptake and subsequent collagenase deficiency, leading to impaired connective tissue catabolism and gingival enlargement; (2) inhibition of aldosterone synthesis, causing increased adrenocorticotropic hormone (ACTH) levels, which stimulate fibroblast proliferation and collagen production.

- *Inflammatory pathways* include upregulation of proinflammatory cytokines and keratinocyte growth factor (KGF).

Trigger of Signal

While the term "gingival hyperplasia" is already listed in the local package insert[3], this review was prompted by Malaysia's notably high ranking in global adverse drug reaction (ADR) reports of gingival enlargement.[2] In the WHO international ADR database*, **Malaysia ranks third** in the number of cases reporting ***gingival hypertrophy#*** (including ***gingival hyperplasia^***) and ***gingival swelling#*** (**n=233**, 9%) following the initiation of amlodipine treatment, after the United Kingdom (n=357, 14%) and the United States (n=278, 11%). The *disproportionality* of these reports is nearly eight times higher than expected (IC_{025}=3.0, $N_{observed}$=233, $N_{expected}$=26). Since 2018, the number of cases reported in Malaysia each year has consistently ranged from 25 to 35. Furthermore, amlodipine accounts for nearly half of the total ADR reports (233/471) received by NPRA involving ***gingival hypertrophy# or gingival swelling#***.

The **Medical Dictionary for Regulatory Activities (MedDRA)** is a standardised international terminology used for sharing regulatory information on medical products. There are five levels to the MedDRA hierarchy, arranged from very specific to very general.

^***Lower-Level Terms (LLTs):*** The most specific level, reflecting how an observation might be reported in practice.
#***Preferred Terms (PTs):*** Standardised terms representing medical concepts, such as a symptom, disease diagnosis, or therapeutic indication. Each PT has at least one LLT.

Local Reports[1,2]

The **233 reported cases** of gingival enlargement following amlodipine use involved patients aged 27 to 80 years, with a mean age of 50.7 years. The majority (65%) were female. Of the 152 cases which reported time-to-onset, over half (59%) experienced gingival enlargement within the first three months after starting amlodipine treatment, with daily doses ranging from 2.5mg to 10mg. However, late presentation is possible.[5] We received 22 reports of gingival enlargement occurring after 2-8 years of amlodipine use. Co-suspected or concomitant drugs were reported in 89 cases, mostly antihypertensives, antidiabetics, and statins, which are not commonly linked to gingival enlargement.

A positive dechallenge was reported in 112 cases (48%), while dechallenge outcomes were unknown in 97 cases. In three cases, patients reported a positive rechallenge. Approximately half of the patients (118/233) had recovered or were in recovery at the time of reporting, with about 5% reporting recovery with sequalae. The remaining 20 cases reported non-recovery, and 95 cases had unknown outcomes.

Conclusion & Advice

In general, drug-induced gingival enlargement has a good prognosis and is reversible upon discontinuing or substituting the offending drug.[9] However, ***many patients, as noted in the local reports, were unaware of the potential link between amlodipine and symptoms like gum swelling.*** As a result, some delayed seeking medical or dental care until their condition worsened, while others informed their clinician only at their next appointment. In one case, the condition progressed to the point where tooth extraction was necessary.

Given the low utilisation of oral healthcare in Malaysia[10], **patient education is crucial for early detection and prevention of complications.** Therefore, healthcare professionals are advised to educate patients about this risk before starting amlodipine, to encourage timely symptom-reporting and reduce the risk of severe outcomes.

*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.

References:

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Features

Training

Pharmacovigilance in the Pharmaceutical Industry: *Latest updates from NPRA*

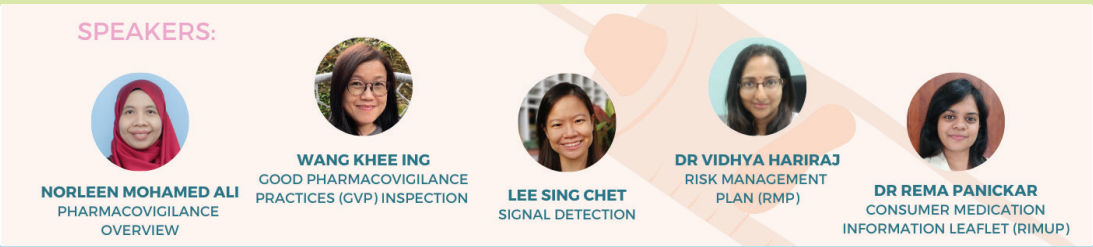
Pharmacovigilance is a rapidly evolving field, and it is vital for all those involved to keep updated on the latest practice. This makes training extremely important, be it for clinicians, personnel from the pharmaceutical industry, academicians and regulators.

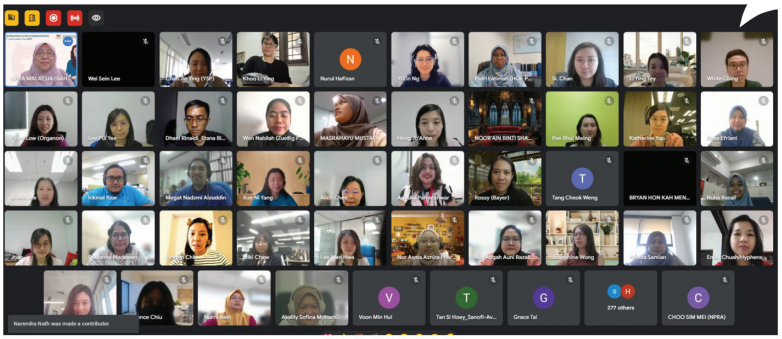
In October 2024, the NPRA Pharmacovigilance Section conducted a seminar specifically for the pharmaceutical industry. As the owners or caretakers of the products, the pharmaceutical industry play a vital role in ensuring the safety of medicines.

The aim of this seminar was to enhance the quality of pharmacovigilance activities carried out by the pharmaceutical industry. NPRA covered five topics during the seminar, as shown in the figure below.

We received many interesting questions, overall positive feedback, and some suggestions to improve our future seminars. There were also many requests for further sessions focused on specific topics of interest. NPRA has started planning for these.

As Malaysia heads towards implementing Good Pharmacovigilance Practice (GVP) Inspections, we hope the pharmaceutical industry will equip itself with the necessary knowledge and skills. Do reach out to us via email (fv@npra.gov.my) if there are any areas of training we can help with.





★★★★★

This is really a great seminar and updates from NPRA. I hope that NPRA can have more seminar like this or workshop where provide a more in-depth knowledge for a specific topic.

★★★★★

Thank you for the fruitful session. Looking forward to continuous engagement between NPRA and industry for PV.

Features

#MedSafetyWeek 2024: *The Malaysian story in pictures*

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 campaign ran from 4 to 10 November 2024, involving more than 90 countries.

This year marked Malaysia's fourth consecutive year of participation in **the MedSafetyWeek** campaign. As we strive to expand our outreach, a special taskforce was established comprising officers from the Pharmacy Practice & Development Division and NPRA. The impact of this teamwork was immediately seen! This year, the MedSafetyWeek social media posts have been shared by health facilities and individuals all across Malaysia, from Johor right up to Perlis. The Malaysian Pharmacists Society (MPS) and several pharmaceutical companies also shared the MedSafetyWeek poster and information.

We will let the photos speak for themselves...

The National #MedSafetyWeek Taskforce

Press Release & Media Coverage

KENYATAAN MEDIA
KEMENTERIAN KESIHATAN MALAYSIA

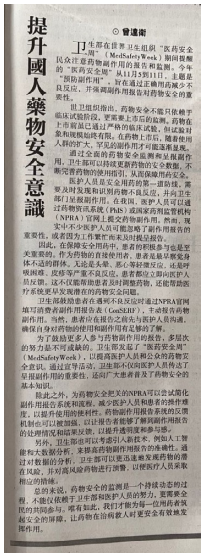
PELANCARAN MINGGU KESELAMATAN UBAT
#MedSafetyWeek 2024

Kementerian Kesihatan Malaysia (KKM) melalui Bahagian Regulatori Farmasi Negara (NPRA) sedang mengambil bahagian dalam kempen tahunan #MedSafetyWeek kali ke-9 yang berlangsung dari 4 hingga 10 November 2024. Kempen peringkat global ini diterajui oleh Pertubuhan Kesihatan Sedunia (WHO) dengan melibatkan 101 organisasi di 90 buah negara. Tema bagi kempen #MedSafetyWeek 2024 pada kali ini adalah *"Preventing Side Effects"* yang menekankan kepentingan penggunakan ubat dengan cara yang betul seperti yang diarahkan oleh anggota kesihatan bagi mencegah kesan sampingan dan juga menitikberatkan keperluan melaporkan kesan sampingan apabila ianya berlaku.

Keselamatan pesakit merupakan keutamaan KKM dan melalui kempen #MedSafetyWeek ini, anggota kesihatan diingatkan untuk membuat semakan dengan teliti sebelum memberikan ubat manakala pesakit pula diingatkan untuk mematuhi arahan penggunaan ubat dengan tepat. Sepanjang #MedSafetyWeek 2024, orang ramai termasuk anggota

Npra Lancar Minggu Keselamatan Ubat Untuk Galakkan Pelaporan Kesan Sampingan Ubat, Vaksin

Anggota kesihatan diingat lapor kesan advers ubat – KKM



提升國人藥物安全意識

THE STAR, TUESDAY 12 NOVEMBER 2024

Ensuring drug safety a collaborative process

THE Health Ministry (MOH) issued a significant message during MedSafetyWeek, held from Nov 5 to 11, urging the public to actively report and monitor medication side effects. This aligns with MedSafetyWeek's 2024 theme "Preventing Side Effects" that is aimed at reducing adverse drug reactions (ADR) through proper usage, and reinforcing the importance of reporting side effects.

While medications are rigorously tested and approved by the National Pharmaceutical Regulatory Agency (NPRA), the limited number of trial participants means that not all potential side effects can be detected. Post-market monitoring captures data from a larger user base, enabling manufacturers to identify side effects that may not have been observed during trials. With this data, the MOH, through the NPRA, can update safety information and refine guidelines to ensure medications are used safely.

Patients play a vital role in medication safety. As the primary users, patients are the first to detect any discomfort. Whether experiencing mild side effects like dizziness or nausea, or more severe reactions like breathing difficulties or rashes, patients should report all symptoms to their healthcare providers promptly. This not only allows for treatment adjustments but also aids in early detection of broader safety issues with drugs.

Healthcare workers are essential in this process, acting as primary contacts for patient concerns, identifying ADRs, and reporting them to the NPRA. However, in practice, some healthcare workers may overlook the importance of reporting or lack the time for timely submissions.

To foster a culture of medication safety, both patients and healthcare workers must work together to ensure that adverse reactions are identified, reported, and managed swiftly.

To further support this effort, the NPRA could simplify the reporting process, making it more user-friendly for both healthcare providers and patients. Enhancing feedback mechanisms would allow those reporting side effects to track their submissions and receive updates on outcomes, increasing transparency and encouraging participation.

Additionally, the MOH could consider leveraging technologies like artificial intelligence (AI) and big data analytics to improve the accuracy of side effect reporting. By analysing this data with AI, the MOH can identify medication-related risks more quickly and issue timely warnings, enabling healthcare providers to take proactive measures.

DAVID CHANG and DR SEAN THUM
Johor Baru

MPS iBulletin

MPS-iBulletin 241108

(Broadcast date: 8 November 2024)

JOM SERTAI #MEDSAFETYWEEK 2024 UNTUK KESELAMATAN UBAT DAN VAKSIN YANG LEBIH BAIK

Jom sertai kami untuk menjayakan kempen #MedSafetyWeek!
Minggu Kesedaran Keselamatan Pengubatan (Medication Safety Week) disambut pada tarikh 4-10 November.

Dengan mengambil ubat seperti yang diarahkan dan melaporkan kesan sampingan yang disyaki, anda boleh membantu kami memastikan ubat-ubatan lebih selamat untuk kita semua

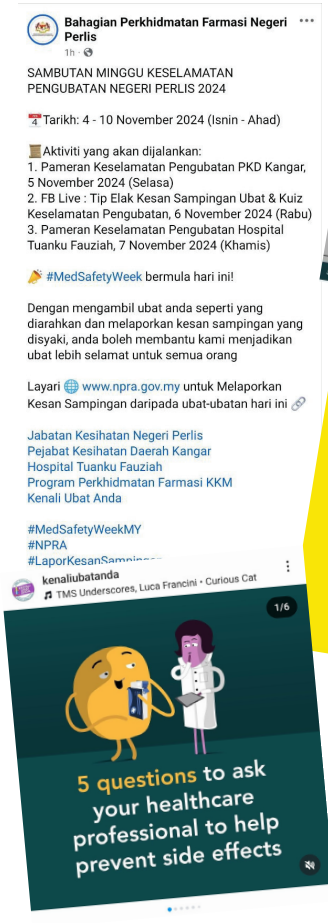
Berbincanglah terlebih dahulu dengan anggota kesihatan anda mengenai kesan sampingan sama ada ubat atau vaksin yang dialami sebelum melaporkannya kepada NPRA melalui www.npra.gov.my

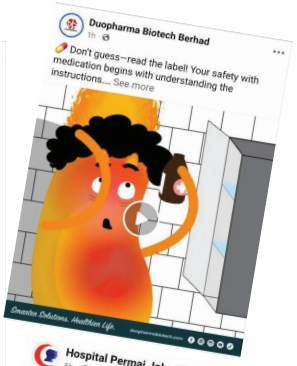
Tingkatkan kesedaran anda mengenai pencegahan dan pelaporan kesan sampingan ubat dan juga vaksin.

#MedSafetyWeek

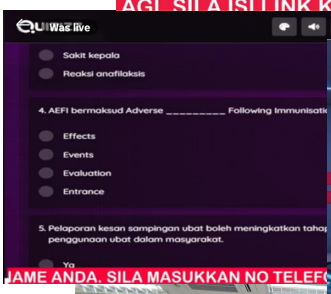
Radio & TV Interviews

Social Media

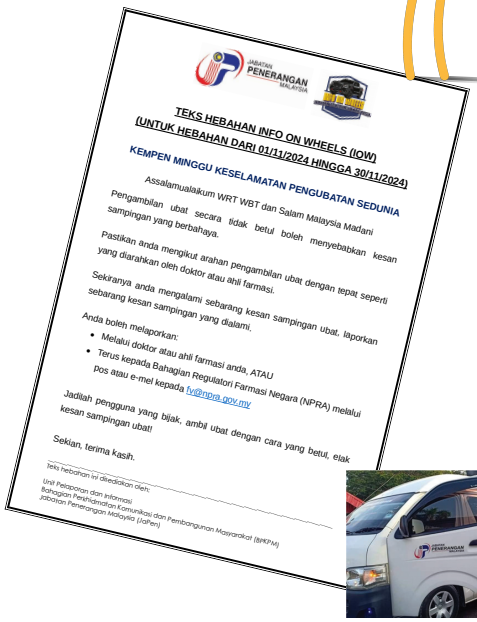




Perlis: Exhibition, FB Live, Quiz



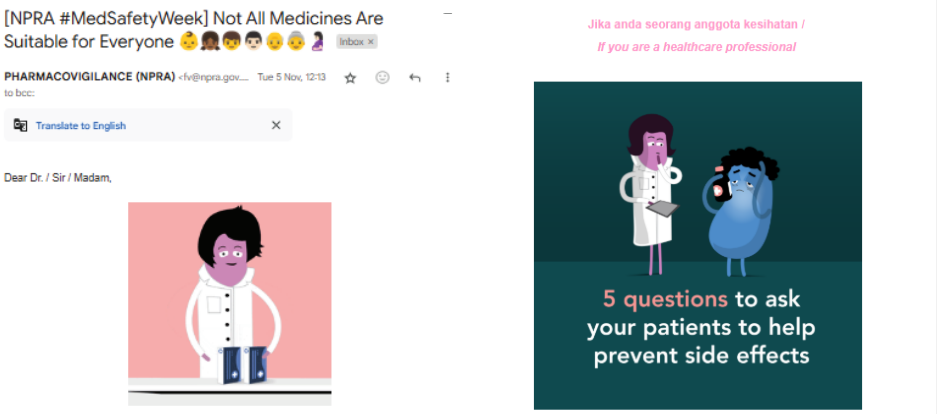
Info on Wheels

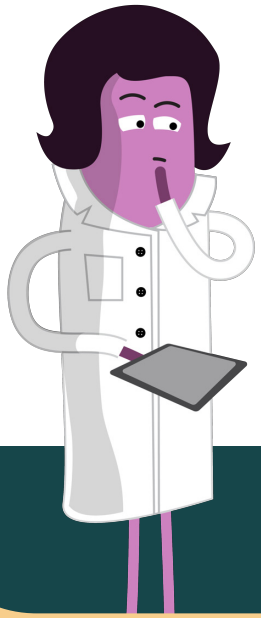


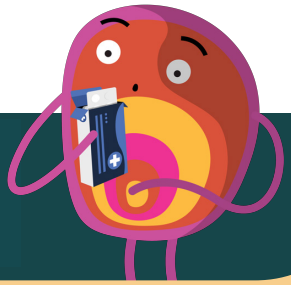
Videos & Poster

NPRA Website

Email Blast







#MedSafetyWeek
4–10 November 2024

Features

Thank you MADRAC 2022-2024

As the curtains draw close on year 2024, we would like to extend our gratitude to the MADRAC members appointed for the 2022-2024 session. This was a challenging period, as we navigated through the post-pandemic era while striving to ensure medicine safety. We truly appreciate the expert opinions, clear advice, and constant support from our MADRAC members throughout the years. *Thank you!*

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

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NPRA Safety Information Mailing List

To join the mailing list:

a) scan the QR code to complete the **subscription form** available on the NPRA website, or

b) send an email with your details to **fv@npra.gov.my**