Ministry of Health, Malaysia
National Pharmaceutical Regulatory Agency

MADRAC Newsletter

For healthcare professionals only

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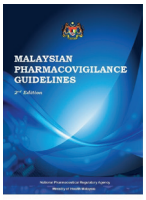
In this Issue

What's New in Pharmacovigilance?



Malaysian Pharmacovigilance (PV) Guidelines
2nd Edition
Released in September 2016
See page 7 of this bulletin for more details...

Vaccine Pharmacovigilance Guidelines for Healthcare Professionals
2nd Edition
Released in August 2016
See page 7 of this bulletin for more details...

NPRA MALAYSIA
http://npra.moh.gov.my

Regulatory Matters

Olanzapine: Risk of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Recently, the antipsychotic drug olanzapine has been associated with the risk of DRESS. The NPRA has completed the review on this risk and a product package insert (PI) update for all olanzapine-containing products was initiated to reflect the latest safety information.

Background of the safety issue

In May 2016, NPRA received information from the United States Food and Drug Administration (U.S. FDA) and the European Medicines Agency (EMA) regarding the risk of olanzapine-related Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). A review of the FDA Adverse Event Reporting System (FAERS) revealed **23 cases** of DRESS associated with olanzapine use[2]. The **median time-to-onset** for the cases reported was **19 days** after initiation of olanzapine, and the median duration of treatment was **two (2) months**. The median dose of olanzapine was reported to be 20 mg daily, though there were also adverse events occurring at **doses as low as 5 mg daily**.

Majority of the cases reported to have **serious outcomes**, in which **18 patients** required medical treatment at hospitals. One (1) case had a positive rechallenge, i.e. reaction reappeared after reintroducing drug; while nine (9) other cases had positive dechallenges, i.e. reaction subsided after drug was stopped or the dose was reduced. In addition to this, six (6) cases reported a positive confirmatory test result in response to olanzapine's drug reaction. The tests involved included drug lymphocyte stimulation test, patch test and lymphocyte transformation test.

Local Scenario

In Malaysia, there are currently **26 products** containing olanzapine registered with the Drug Control Authority (DCA). These products are available as film-coated tablets and orodispersible tablets.

Since year 2000, the NPRA has received **283 ADR reports** with **488 adverse events** suspected to be related to olanzapine. There were **four (4) reports (0.8%)** involving **severe cutaneous adverse reactions (SCARs)**, namely **erythema multiforme (3)** and **DRESS (1)**.

NPRA has reviewed this safety issue and a directive [*Ruj: Bil (5) dlm. BPFK/PPP/07/25 Jld. 1*] was issued for all local package inserts of olanzapine-containing products to be updated with information on the risk of DRESS.

References

1. Choudhary et al. (2013). Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome. J Clin Aesthet Dermatol; 6(6): 31-37.
2. US FDA (2016). Olanzapine: Drug Safety Communication – FDA Warns About Rare But Serious Skin Reactions.
3. The National ADR Database, NPRA [Accessed October 2016].

Advice to Healthcare Professionals

- If DRESS is suspected, stop treatment with olanzapine. Management of DRESS includes early recognition of the symptoms, discontinuation of the offending drug and supportive care.
- **Counselling**: Advise patients taking olanzapine to seek medical attention if they experience the following symptoms: fever, rash, swollen lymph glands, or face swelling. Patients also should be advised not to stop their medication or change the dose without consulting a healthcare professional.
- Report any ADR suspected to be related to olanzapine-use to the NPRA.

Regulatory Matters

Codeine: Risk of respiratory depression

Codeine-containing medicines can lead to respiratory problems in sensitive patients[1]. At risk are children under 12 years of age, babies of breastfeeding mothers who take codeine, as well as patients who are 'ultra-rapid metabolisers' (have the metabolic capability to convert codeine into morphine at a faster rate than normal).

Background of the safety issue

In July 2016, NPRA received information about a Dear Healthcare Professional Communication Letter (DHPCL) approved by the Health Sciences Authority (HSA), Singapore, to inform healthcare professionals of new restrictions on the use of codeine-containing products in children, to minimise the risk of death and respiratory depression.

Previously, the European Medicines Agency (EMA) had conducted a review on codeine-containing products and the risk of respiratory depression. This review was triggered by concern regarding opioid toxicity in children and the lack of consistent risk minimisation measures taken. Cases were described in the literature of fatal or life-threatening respiratory depression when codeine was given to children after adenoidectomy/tonsillectomy for obstructive sleep apnoea.

The risk of respiratory depression in children has been linked to genetic polymorphism and codeine metabolism. Patients who are CYP2D6 ultra-rapid metabolisers are found to convert codeine to morphine at a faster rate, resulting in toxic levels of morphine in the blood. The unpredictable and variable metabolism in children, governed by CYP2D6 polymorphism, may cause some children to exhibit morphine-related serious adverse events such as breathing difficulties or respiratory depression even within the recommended doses.

Local Scenario

In Malaysia, there are currently **six (6) products** containing codeine registered with the Drug Control Authority (DCA). These products are available as tablets in combination with paracetamol. No syrup formulation containing codeine has been registered since 1996, as codeine is not allowed as an ingredient in cough syrup according to the Drug Registration Guidance Document (DRGD).

Since year 2000, the National ADR Monitoring Centre, NPRA has received **16 ADR reports** with 32 adverse events suspected to be related to codeine. Three (3) reports were associated with breathing problems, namely **shortness of breath (2)** and **breathing difficulty (1)**.

NPRA has reviewed this safety issue and a directive [*Ruj: Bil (2) dlm. BPFK/PPP/07/25 Jld. 1*] was issued for all local PIs of codeine-containing products to be updated with information on the risk of respiratory depression.

References

1. Swissmedic (2015). Risks of preparations containing codeine intended for the treatment of coughs and colds.
2. EMA (2015). Codeine-containing medicinal products for the treatment of cough or cold in paediatric patients.
3. The National ADR Database, NPRA [Accessed August 2016].

Advice to Healthcare Professionals

- Codeine is now **contraindicated** in the following patient groups:
  - Children aged below 12 years for the symptomatic treatment of colds.
  - All paediatric patients (0 to 18 years of age) who undergo tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome.
  - Women who are breastfeeding.
  - Patients who are known CYP2D6 ultra-rapid metabolisers.
- Please report any ADR suspected to be related to codeine-use to the NPRA.

Regulatory Matters

Warfarin: Risk of calciphylaxis

Warfarin is an oral anticoagulant which acts by inhibiting the synthesis of vitamin K-dependent clotting factors II, VII, IX, and X[1].

Calciphylaxis, also known as calcific uremic arteriolopathy, is a rare syndrome of vascular calcification with cutaneous necrosis[1]. Calciphylaxis is associated with high morbidity and mortality (60-80%) resulting primarily from local and systemic infections[2,3]. This condition is mostly observed in patients with end-stage renal disease, or those with known risk factors, such as protein C or S deficiency, hyperphosphatemia, hypercalcaemia or hypoalbuminaemia[1].

Rare cases of calciphylaxis have been reported in patients on warfarin therapy. Although many of the cases reported pre-existing renal disease, some noted normal renal function[1].

In May 2016, the European Medicine Agency (EMA)'s review concluded that there is a reasonable possibility of a causal relationship between calciphylaxis and the use of warfarin.

Potential Mechanisms

The exact pathogenesis of calciphylaxis remains poorly understood. Warfarin-induced calciphylaxis could be mediated through the matrix Gla protein, which is a vitamin K-dependent protein involved in the inhibition of calcification. As warfarin inhibits this protein, it promotes vascular calcification[1].

Local Scenario

There are currently **five (5) registered products** containing warfarin in Malaysia, all in tablet formulation. Warfarin is approved for treatment/prevention of deep vein thrombosis and pulmonary embolism as well as prevention of thromboembolic complications.

ADR Reports

Since year 2000, the NPRA has received **341 warfarin-related ADR reports** with a sum of **563 adverse events**. Most of the adverse events were made up of skin and subcutaneous tissue disorders (111 cases, 19.7%), nervous system disorders (92 cases, 16.3%) and gastrointestinal system disorders (63 cases, 11.2%)[4].

At present, no reports of calciphylaxis have been received locally. One report described a female patient who developed pain and skin necrosis after taking warfarin, however it was not confirmed whether this was calciphylaxis or warfarin-induced skin necrosis (WISN), as no skin biopsy was done.

All products containing warfarin are required to **update their packaging insert** with information on the risk of calciphylaxis as mentioned in the DCA directive issued on 11 October 2016 [*Ruj: (1) dlm BPFK/PPP/07/25 Jld 1*].

References

1. Medicines and Healthcare Products Regulatory Agency (2016). Drug Safety Update. Warfarin: reports of calciphylaxis. https://www.gov.uk/drug-safety-update/warfarin-reports-of-calciphylaxis
2. Mazhar, AR et al (2001). Risk Factors and Mortality Associated With Calciphylaxis in End-stage Renal Disease. Kidney International 60: 324-332.
3. Saifan, C et al (2013). Warfarin-induced Calciphylaxis: A Case Report and Review of Literature. International Journal of General Medicine 6: 665-669.
4. The National ADR Database, NPRA. [Accessed September 2016].

Advice to Healthcare Professionals

- Calciphylaxis is a rare but serious condition which is normally seen in patients with known risk factors such as end-stage renal disease.
- Calciphylaxis cases have been reported in patients taking warfarin including those with normal renal function.
- If calciphylaxis is diagnosed, appropriate treatment should be started and consideration should be given to stopping warfarin treatment.
- Please report any ADR suspected to be related to warfarin-use to the NPRA.

Regulatory Matters

Advice on the risk of lower limb amputation during treatment with Invokana® (canagliflozin)

Canagliflozin is one of the sodium glucose co-transporter 2 (SGLT2) inhibitors that is used for the management of Type II Diabetes mellitus. As adjunct to diet and exercise, canagliflozin is a once daily tablet that can be used as monotherapy or in combination with other antidiabetic medications to reduce blood glucose levels.

Background of the safety issue

In the ongoing Canagliflozin Cardiovascular Assessment Study (CANVAS) long-term clinical trial, the independent data monitoring committee identified an increased risk of lower limb amputations, mostly affecting the toes. It was found that the amputations occurred about **twice as often** in patients treated with canagliflozin (7 per 1,000 patient years in the canagliflozin 100mg group, and 5 per 1,000 patient years in the canagliflozin 300mg group) compared with 3 per 1,000 patient years in the placebo group.

Patients with diabetes (especially those with poorly controlled diabetes and pre-existing cardiovascular problems) are at increased risk of infection and ulceration which can result in lower limb amputations. No increase in such amputations was seen in 12 other completed clinical trials with canagliflozin. Another ongoing study, CANVAS-R, which involves patient groups similar to CANVAS, showed a small and **non-statistically significant** increase in the number of amputations for patients on canagliflozin.

The possibility that canagliflozin increases lower limb amputations is **currently not confirmed** as cases of lower limb amputation have occurred in both the canagliflozin and placebo groups in the trial. The European Medicines Agency (EMA) and the United States Food and Drug Administration (U.S. FDA) are currently evaluating the risk of lower limb amputation associated with canagliflozin and will communicate the evaluation results once the review is completed.

While the mechanism behind these events has not been ascertained, dehydration and volume depletion may be contributory factors.

Local Scenario

Invokana® 100mg and 300mg tablets were recently registered in Malaysia in 2016. At the time of this publication, the NPRA has not received any ADR reports related to these products.

In agreement with NPRA, the product registration holder of Invokana® has issued a Direct Healthcare Professional Communication (DHPC) letter on this matter. The local PI of Invokana® will be updated with information on the risk of lower limb amputation during treatment with canagliflozin-containing products.

References

1. US FDA (2016). Interim clinical trial results find increased risk of leg and foot amputations, mostly affecting the toes, with the diabetes medicine canagliflozin (Invokana, Invokamet).
2. EMA (2016). EMA reviews diabetes medicine canagliflozin
3. The National ADR Database, NPRA [Accessed August 2016].

Advice to Healthcare Professionals

- **Counselling**: Emphasise the importance of routine footcare, and advise patients to seek medical attention if they experience pain, soreness, discolouration, ulceration or infections of their legs or feet.
- Patients should be educated on the signs and symptoms of volume depletion, and advised to always remain hydrated.
- As a precautionary measure, stopping canagliflozin treatment may be considered if a patient develops a significant complication, such as a lower-extremity skin ulcer, osteomyelitis or gangrene, at least until the complication has resolved.
- Report suspected adverse drug reactions related to canagliflozin to the NPRA.

Regulatory Matters

List of Direct Healthcare Professional Communication (DHPC) Letters for 2016

Direct Healthcare Professional Communication (DHPC) letters are issued by product registration holders with the approval of NPRA, to disseminate information on particularly important safety issues or changes in product prescribing information.

List of DHPCs approved by NPRA for distribution in 2016

04 Feb
Xgeva® 120mg Solution for Injection (denosumab)
Prolia® Solution for Injection 60mg (denosumab)
Clinically Significant Cases of Hypercalcaemia after Cessation of Treatment with Denosumab in Paediatric Patients.

03 Mar
Viekirax® (ombitasvir/ paritaprevir/ ritonavir)
Exviera® (dasabuvir)
Viekirax and Exviera not recommended in Child-Pugh B Patients.

30 Mar
Xalkori® (crizotinib)
Inclusion of a new warning regarding cardiac failure.

25 Apr
Glivec® (imatinib)
Tasigna® (nilotinib)
Risk of hepatitis B reactivation.

18 May
Locabiotal® Solution (fusafungine)
Withdrawal of registration following European Medicines Agency's benefit-risk assessment.

01 July
Tarceva® (erlotinib)
First-line maintenance indication now restricted to treatment of patients whose tumours harbour an EGFR-activating mutation.

22 July
Adempas® (riociguat)
New contraindication for patients with pulmonary hypertension associated with idiopathic interstitial pneumonias (PH-IIP).

25 Aug
Invokana® (canagliflozin)
Advice on the risk of lower limb amputation (primarily of the toe) during treatment with canagliflozin-containing medicines.

14 Nov
Implanon NXT® (etonogestrel)
Implants have been found rarely in the vasculature and lung. An update on possible risks and complications regarding insertion, localisation, removal and migration.

14 Dec
Zaltrap® (aflibercept)
Information on the Risk of Osteonecrosis of the Jaw.

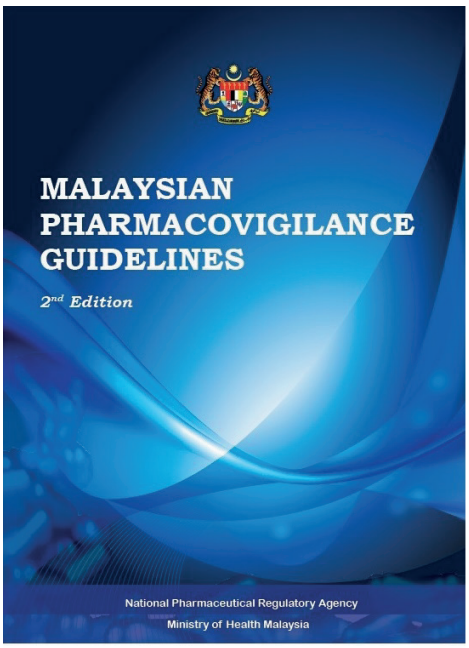
What's New?

Malaysian Pharmacovigilance Guidelines (2016)

In September 2016, NPRA published the Malaysian Pharmacovigilance Guidelines (2nd edition) to align with current international requirements in adverse drug reaction (ADR) reporting and safety monitoring of medicinal products.

This guidance document has been updated since its first publication in 2002, to include detailed information on ADR reporting for healthcare professionals and product registration holders (PRHs).

NPRA hopes that this guideline will serve as a reference for healthcare professionals and PRHs to keep abreast with current pharmacovigilance practices and overall, to ensure the safety profile of registered medicinal products in Malaysia.



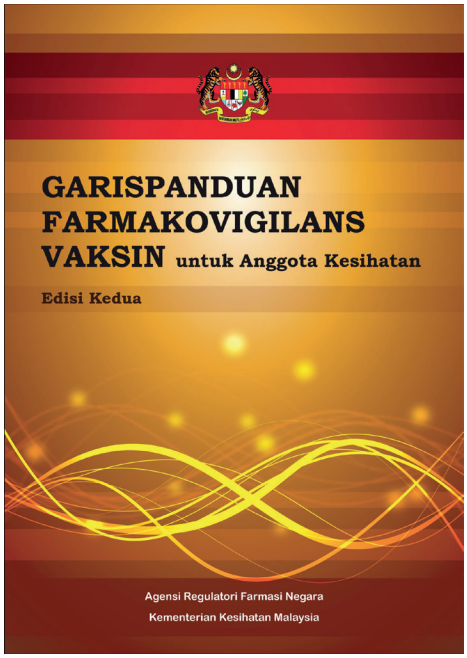
Vaccine Pharmacovigilance Guidelines for Healthcare Professionals (2016)

The Pharmacovigilance Guideline for Vaccines was first published in 2010 with the aim to educate healthcare professionals on the classifications of adverse events following immunisation (AEFI), reporting of AEFIs and management of AEFIs.

With the release of its second edition in August 2016, new updates have been incorporated into the guideline to address serious AEFI cases and management of serious AEFIs.

Key updates include:

- Definition and examples of serious AEFIs.
- Integrated workflow for the management of serious AEFI cases.
- Guidance for healthcare professionals on AEFI reporting.
- Distinction of AEFI forms intended for healthcare professionals and vaccinees.



To download the free full text online, click on the images or visit:
http://npra.moh.gov.my > Guidelines Central > Reporting and Monitoring (MADRAC).

What's New?

Preparing for Pharmacovigilance Inspection

The NPRA is heading towards conducting pharmacovigilance (PV) Inspection in Malaysia. PV Inspection is conducted by health regulatory authorities on product registration holders to determine compliance with regulatory PV obligations.

An introductory training session was held in August 2015 for participants from pharmaceutical companies to gain insight and understanding on PV inspections and the role of a local PV officer.

The NPRA is taking several steps in our effort to establish a competent PV Inspectorate. In August 2016, NPRA PV staff were given an overview on this topic by an Expert Inspector of Good Pharmacovigilance Practice from the United Kingdom (UK) Medicines and Healthcare Products Regulatory Agency (MHRA). The PV staff received further training in November 2016, from representatives of the UK MHRA PV Information & Signal Management Unit, in a two-day course coordinated by the World Health Organisation (WHO).

The next stage will be for selected staff to attend fellowship training as observers for PV inspection in the UK, scheduled in mid-2017. The Malaysian PV Guidelines will then be updated with requirements for the PV System Master File and PV Inspection. Actual implementation of PV Inspection in Malaysia will be carried out in stages, targeted to begin in 2018.

For Healthcare Professionals

How to report adverse drug reactions?

NPRA encourages the reporting of all suspected adverse drug reactions to medicines, including vaccines, over-the-counter medicines, as well as traditional products and health supplements.

To report adverse drug reactions:

1. Visit **npra.moh.gov.my**
2. Click on **ADR Reporting**
3. Go to report as a healthcare professional online or via hardcopy.
4. Submit the form once completed.

Completed forms may be submitted via email, post, or fax to:

The Pharmacovigilance Section,
National Pharmaceutical Regulatory Agency (NPRA),
Ministry of Health, Malaysia.
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