

MADRAC *Bulletin*

For healthcare professionals only

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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 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.



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Signals



- **Ribociclib and Blood Creatinine Increased** ... 2

Features



- **New! Infographic of Paracetamol: Reports of Fixed Drug Eruptions** ... 4

Articles Based on Case Reports



- **Methotrexate-Induced Posterior Reversible Encephalopathy Syndrome (PRES) in a Paediatric Patient** ... 5

What's New



- **List of Safety Alerts/Directives Related to Drug Safety Issues** ... 7

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 signal and 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 signals presented below are intended to raise awareness of reported adverse events and stimulate additional reporting from healthcare professionals.

A safety signal, according to the WHO-Uppsala Monitoring Centre (UMC) definition³, refers to information on a new or known side effect that may be caused by a medicine and is typically generated from more than a single report of a suspected side effect. It is important to note that a signal does not indicate a direct causal relationship between a side effect and a medicine, but is essentially only a hypothesis that, together with data and arguments, justifies the need for further assessment.

Ribociclib and Blood Creatinine Increased

Written by Dr. Vidhya Hariraj; Reviewed by Nora Ashikin Mohd Ali

Trigger of Signal

During our routine signal detection activity, NPRA has detected a disproportionality in the reporting of **blood creatinine increased associated with ribociclib** ($IC_{025}=1.9$).² As of January 2024, NPRA has received 7 reports.¹ Globally, there were 364 cases reported.²

Local Reports¹

The seven local reports involved four females while three others did not report the gender. Three cases were within the age range of 45 to 64 years old, while age was not specified in the remaining four reports. Three cases were identified to be serious. Two recovered with sequelae, while the outcome was not specified in five reports. Letrozole, metformin and gliclazide were co-reported in three separate cases. Other details such as time-to-onset, dechallenge/rechallenge, and other medically important conditions were not reported in almost all cases. All seven reports were assigned causality *C3 possible*.

Background

Ribociclib is indicated for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with:

- an aromatase inhibitor as initial endocrine-based therapy in pre/perimenopausal or postmenopausal women or in men; or
- fulvestrant as initial endocrine-based therapy or following disease progression on endocrine therapy in postmenopausal women or in men.⁴

Ribociclib is a cyclin dependent kinase 4/6 (CDK 4/6) inhibitor which targets and blocks specific proteins within the breast cancer cells that make them multiply. It comes as a tablet to be taken orally.⁴

In terms of mechanism, ribociclib may cause an increase in blood creatinine through inhibition of the renal transporters organic cation transporter 2 (OCT2) and multidrug and toxin extrusion protein 1 (MATE1), which are involved in the active secretion of creatinine from the proximal tubules.⁵ Blood creatinine increase associated with ribociclib has been observed in the following clinical trials: MONALEESA-2 (ribociclib in combination with letrozole), MONALEESA-3 (ribociclib in combination with fulvestrant), and MONALEESA-7 (ribociclib in combination with an aromatase Inhibitor) as laboratory abnormalities and are addressed in the Malaysian Package Insert for ribociclib.⁴

Conclusion & Advice

Blood creatinine increase in association with ribociclib is *plausible*. Based on the local product package insert for ribociclib, no dose adjustment is necessary in patients with **mild or moderate** renal impairment. For patients with **severe** renal impairment, the recommended starting dose is 200 mg ribociclib once daily.⁴

Healthcare professionals are encouraged to be vigilant and report any suspected cases with more clinical information to the NPRA.

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*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.



Image created by OpenAI's DALL-E

Features

For healthcare professionals

PARACETAMOL: Reports of Fixed Drug Eruptions

Paracetamol is **very rarely** associated with **fixed drug eruptions (FDEs)**.

99

total reports in
Malaysia*

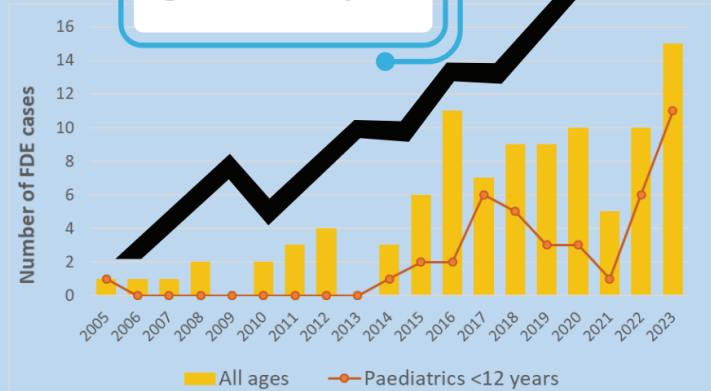
41%

in children aged
below 12 years

* From Jan 2005 - Mar 2024

WHAT'S NEW?

Increasing trend
particularly
involving children
aged below 12 years



PLEASE REMIND PATIENTS (OR THEIR CAREGIVERS) :

- ✓ to **watch out** for these early signs and symptoms of FDE:
skin reddening, blisters, rash.
- ✓ to **STOP** using the medicine immediately and seek **medical attention** if these signs and symptoms occur.

Where to
report?



scan here to download
the ADR form

REPORT

Please report **any** adverse events
to the **NPRA**.



National Pharmaceutical Regulatory Agency
Ministry of Health, Malaysia

Your reports will help
the NPRA to take steps
to reduce the risk.

Any queries?

Please send us an email:
fv@npra.gov.my

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.

Methotrexate-Induced Posterior Reversible Encephalopathy Syndrome (PRES) in a Paediatric Patient

By Sabariah binti Pakeer Oothuman

Case Report¹

A 6-year-old patient weighing 14.3 kg with underlying T-cell acute lymphoblastic leukaemia was given intravenous (IV) methotrexate 3.3 g and intrathecal methotrexate 12.5 mg, along with IV vincristine and IV granisetron (as an antiemetic). After 62 hours of initiating therapy, the patient experienced seizures, hallucinations, and visual impairment. He was also reported to have raised blood pressure, and acute kidney failure. His methotrexate blood level was high at 42.8 $\mu\text{mol/L}$ (normal range: $<0.4 \mu\text{mol/L}$). The patient was diagnosed with **posterior reversible encephalopathy syndrome (PRES) induced by methotrexate toxicity**. Methotrexate was since withheld and the patient was treated with IV midazolam. A computed tomography (CT) brain scan conducted a week after the incident showed no intracranial bleed or brain parenchymal lesion. The patient made a full recovery from the incident. Due to the presence of concomitant drugs, the adverse event was given a causality *possibly-related* to methotrexate.

Discussion

Methotrexate is an anti-metabolite mainly used in chemotherapy along with other agents. It may also be used as an immunosuppressive agent in autoimmune diseases such as rheumatoid arthritis and psoriasis.² In Malaysia, there are currently 10 registered products containing methotrexate including both parenteral and oral preparations.³ The use of methotrexate has been associated with neurotoxicity which includes PRES.⁴ It usually takes 5-14 days for acute encephalopathy to develop after intrathecal or high dose methotrexate ($1.5\text{-}8 \text{ g/m}^2$). The encephalopathy normally subsides within a week without permanent neurological effects.⁵

PRES is an acute reversible syndrome typically presenting with episodes of headaches, hypertension, seizures, altered mental status, and/or visual disturbance.^{4,6} It shows characteristic imaging findings of vasogenic oedema mainly in the subcortical white matter of the parietal and occipital lobes.^{5,7,8} Examples of scenarios in which PRES may be seen are (pre)eclampsia, renal disease, and autoimmune disorders, among others.⁷ It has been shown that PRES can occur in any age group. However, the syndrome is uncommon in adults and mostly seen in paediatric oncology patients.

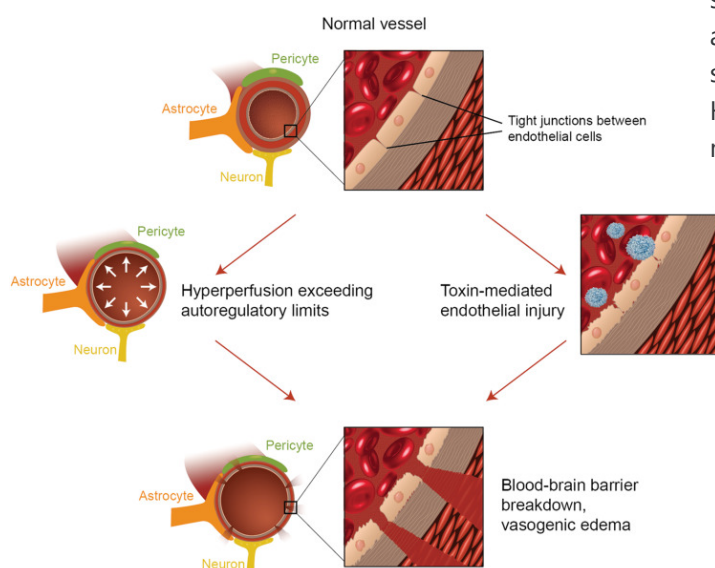


Figure 1: Illustration of the two major theories of the underlying pathophysiology of PRES.⁴

Although the exact mechanism that leads to PRES is not fully understood, two main theories have been proposed, as follow:

- i) hypertension may lead to blood brain barrier breakdown and vascular leakage. This ultimately results in vasogenic oedema.^{5,7,9}
- ii) immunosuppressive or cytotoxic drugs may impact the vascular endothelium and potentially cause endothelial damage.^{6,7} Moreover, chemotherapeutic agents such as methotrexate could contribute to PRES by inducing or aggravating hypertension due to concomitant use of corticosteroids treatment or renal dysfunction.^{4,5}

A timely diagnosis together with immediate and symptom-directed correction of the primary cause of PRES are key to managing this syndrome.⁵ If PRES occurred due to elevated arterial pressure, treatment should be aimed at correcting the increased blood pressure in a controlled manner. In the case of PRES induced by an immunosuppressive agent, tapering or withdrawal of the medication has demonstrated clinical and radiological improvement.^{7,10} Anticonvulsant agents are used in cases where seizures have occurred, however the ideal agent(s), timing, and length of treatment have not been ascertained.⁷

To date, NPRA has received 475 local adverse drug reaction (ADR) reports with 1,043 adverse events suspected to be related to methotrexate.¹ The most commonly reported adverse events involved skin reactions, namely pruritus (40) and rash (39), followed by vomiting (36) and increased alanine aminotransferase (29). There are **four reported cases of PRES involving methotrexate** in Malaysia, including the one discussed in this article. All four cases involved paediatric oncology patients aged between 6 to 10 years.

As of May 2024, the World Health Organisation (WHO) international ADR database has recorded 459 cases of PRES associated with methotrexate use.^{11*} Among these, 262 cases (57.1%) involved patients aged below 18 years.

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Advice for Health Care Professionals

- 1 Be mindful** of the risk of PRES upon initiation of intrathecal methotrexate and high-dose IV methotrexate, particularly in children and patients taking corticosteroids.
- 2 Assess** patient's renal function before starting methotrexate and routinely monitor during therapy.
- 3 Educate** patients and caregivers to watch for the signs and symptoms of PRES (such as headache, seizures, high blood pressure, altered mental status, and visual disturbance) and seek prompt medical advice.
- 4** If symptoms of PRES occur, consider **performing** magnetic resonance imaging (MRI) of the brain to confirm the diagnosis.
- 5** When PRES is suspected, consider **discontinuing or reducing** the dose of methotrexate.
- 6 Report** all adverse events to be related to methotrexate containing products to the NPRA.

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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		Directive Ref. No. [Date]
		Title	Date	
1	Anti-Clusters of Differentiation 20 (CD20) Antibodies (Rituximab, Obinutuzumab, Ofatumumab, Ocrelizumab)	Risk of Pyoderma Gangrenosum	28-Jun-2024	-
2	Hydroxychloroquine	Risk of Sweet's Syndrome (Acute Febrile Neutrophilic Dermatitis)	15-Jul-2024	NPRA.600-1/9/13 (45) Jld.1 [9 Jul 2024]
3	17-Hydroxyprogesterone Caproate (17-OHPC)	Potential Cancer Risk in Offspring Exposed in Utero and Limited Efficacy Data	22-Jul-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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- scan the QR code to complete the [subscription form](#) available on the NPRA website, or



- send an email with your details to fv@npra.gov.my

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