Ministry of Health, Malaysia
National Pharmaceutical Regulatory Agency

MADRAC Newsletter

For healthcare professionals only

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In this Issue

Safety Issues Presented to MADRAC in 2017

Regulatory Matters

- Fluconazole: Risk of Spontaneous Abortion and Multiple Congenital Abnormalities
- Tramadol: Restricted Use in Children and Warnings of Use in Pregnant and Breastfeeding Women
- Metformin: Use in Patients with Moderately Reduced Kidney Function
- Metronidazole: Risk of Hepatotoxicity in Patients with Cockayne Syndrome
- Aripiprazole: Risk of Pathological Gambling and Impulse-Control Problems

ADR Reporting

- CPD Points for Quality ADR Reporting

Safety Issues Presented to MADRAC in 2017

As part of NPRA's efforts to ensure the positive risk-benefit balance of medicinal products registered in Malaysia, safety issues are reviewed to ensure risk minimisation measures are carried out when necessary. Majority of the safety issues reviewed in 2017 were identified through screening of reference regulatory agency websites, such as the European Medicines Agency (EMA) and United States Food and Drug Authority (U.S. FDA), while some were notified to the NPRA by the product registration holders.

Summary of Safety Issues Presented to MADRAC in 2017

5
MADRAC meetings held in 2017

1
Safety issue resulted in suspension of product registration

31
Safety issues presented

8
Direct Healthcare Professional Communication (DHPC) letters

22
Safety issues resulted in package insert updates

1,186
Products involved in regulatory action

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Safety Issues Presented to MADRAC in 2017

Following review, the safety issues are discussed at MADRAC meetings to determine appropriate risk minimisation measures. Regulatory action taken involved updates to the product package inserts (PI).

	Product name (active ingredient) & safety issue	DCA* directive	DHPC*	PI* update	Publication of article	Further review
1	Proton pump inhibitors: Risk of fundic gland polyps (benign)					●
2	Pomalyst® (pomalidomide): Hepatitis B virus status to be established before initiating treatment with pomalidomide		●	●	●	
3	Chlorhexidine: Risk of hypersensitivity reactions	●		●	●	
4	Gadolinium-based contrast agents: Evidence of gadolinium deposits in the brain after magnetic resonance imaging (MRI) body scans but no signs of harm					●
5	Escapelle®, Postinor-2®, Madonna® (levonorgestrel): Interactions with hepatic enzyme inducers and contraceptive efficacy	●	● ●	●	●	
6	Inhaled corticosteroids used for treatment of chronic obstructive pulmonary disease (COPD): Increased risk of pneumonia	●		●	●	
7	Miconazole and warfarin: Safety information related to drug interaction	● ●		●	●	
8	Loperamide: Risk of serious cardiac events with the use of higher than the recommended dose and misuse	●		●	●	
9	Revlimid® (lenalidomide): New important advice regarding viral reactivation		●	●	●	
10	Zelboraf® (vemurafenib): Risk of Dupuytren's contracture and plantar fascial fibromatosis		●	●	●	
11	Domide® (thalidomide): New important advice regarding viral reactivation and pulmonary hypertension		●	●	●	
12	Keytruda® (pembrolizumab): Fatal cases of Stevens-Johnson syndrome and toxic epidermal necrolysis reported with Keytruda®		●	●	●	
13	Tramadol: Restriction of use in children and warning on use in pregnant and breastfeeding mothers	●		●	●	
14	Proton pump inhibitors: Risk of adverse events associated with long-term use	●		●	●	
15	Proton pump inhibitors: Information on elevated circulating levels of Chromogranin A (CgA)	●		●		
16	Etoricoxib: Revised starting dose for treatment of rheumatoid arthritis and ankylosing spondylitis	●		●	●	
17	Hyoscine (injection dosage forms only): Risk of serious adverse effects in patients with underlying cardiac disease	●		●	●	
18	Aripiprazole: Safety information on the adverse effects gambling disorder and impulse-control problems	●		●	●	
19	Testosterone: Safety information on adverse effects associated with abuse and dependence	●		●		
20	Metronidazole (excluding products for external use): Risk of hepatotoxicity in patients with Cockayne syndrome	●		●	●	
21	Metformin: Information on use in patients with moderately reduced kidney function and strengthening the warning on lactic acidosis	●		●	●	
22	Opioids: Risk of serotonin syndrome due to interaction with serotonergic drugs, and the risk of adrenal insufficiency and androgen deficiency following long-term use	●		●		
23	Opioids and benzodiazepines: Information related to drug interaction	●		●		
24	Fluconazole: Risk of spontaneous abortion, and strengthening the safety information on multiple congenital abnormalities and use in breastfeeding women	●		●	●	
25	Modified-release paracetamol: Overdose complex and difficult to manage with modified-release products					●
26	Ribomustin® (bendamustine): Increased mortality observed when used in non-approved combination treatments or outside the approved indications; Monitor for opportunistic infections and hepatitis B reactivation		●	●		
27	Azithromycin and erythromycin (excluding topical/external use products and eye drops): Risk of Infantile Hypertrophic Pyloric Stenosis (IHPS)	●		●		
28	Ambroxol and bromhexine: Risk of anaphylaxis and severe cutaneous adverse reactions (SCARs)	●		●		
29	Cobicistat and corticosteroid (excluding products for external use): Information on drug interaction	●		●		
30	Statins: Information on immune-mediated necrotizing myopathy (IMNM)	●		●		
31	Levetiracetam: Safety information on the risk of acute kidney injury, rhabdomyolysis/blood creatine phosphokinase increased, and encephalopathy	●		●		

*DCA = Drug Authority Control; DHPC = Direct Healthcare Professional Communication; PI = Package insert

Regulatory Matters

Fluconazole: Risk of Spontaneous Abortion and Multiple Congenital Abnormalities

by Wan Noor Ardila Wan Abhar

Background of the safety issue

The NPRA would like to highlight new warnings on the risk of spontaneous abortion in pregnant women on fluconazole therapy, and strengthened warnings on the risk of multiple congenital abnormalities in infants whose mothers were treated with fluconazole.

The risk of spontaneous abortion associated with fluconazole use stemmed from a cohort study in Denmark, which studied the association between oral fluconazole use during pregnancy and the risk of spontaneous abortion and stillbirth. It was found that there was a significantly increased risk of spontaneous abortion associated with oral fluconazole exposure in pregnant women, compared with risk among unexposed pregnant women and women with topical azole exposure in pregnancy.

Following this signal, the European Medicines Agency (EMA) initiated a review on this risk. Considering all available evidence from the assessment of the study, clinical trials, postmarketing data as well as literature publications, EMA's Pharmacovigilance Risk Assessment Committee (PRAC) agreed that the package inserts for all products containing fluconazole of all formulations should be updated with information on this risk.

Registered Products in Malaysia

There are currently 38 products containing fluconazole registered in Malaysia (oral and injectable formulations.

Local ADR Reports

To date, NPRA has received 154 ADR reports with 244 adverse events suspected to be related to fluconazole. Majority of the adverse events involved skin disorders, such as rash and pruritus. To date, no reports on spontaneous abortion or any congenital abnormalities have been received by NPRA.

Regulatory Action

NPRA has reviewed this safety issue and considered that the package inserts and consumer medicine information leaflets of all products containing fluconazole are required to be updated with these warnings, as stated in the Malaysian Drug Control Authority (DCA) directive dated 17 October 2017 [*Ref: Bil (29) dlm. BPFK/PPP/07/25 Jld. 1*], which may be downloaded from the NPRA website.

Advice to Healthcare Professionals

- There have been reports of spontaneous abortion and congenital abnormalities in infants whose mothers were treated with 150 mg of fluconazole as a single or repeated dose in the first trimester.
- Advise female patients of child-bearing potential to practice **effective contraceptive measures** during treatment and one week after completing treatment with fluconazole.
- **Breastfeeding** may be maintained after a single dose of 150 mg fluconazole. However, breastfeeding is not recommended with repeated doses or high dose fluconazole.
- Please report any adverse reactions suspected with the use of fluconazole to the NPRA.

References

1. EMA (2017). PRAC recommendations on signals adopted at the PRAC meeting of 6-9 February 2017 (EMA/PRAC/68642/2017).
2. Ditte Mølgaard-Nielsen *et al.* (2016). Association Between Use of Oral Fluconazole During Pregnancy and Risk of Spontaneous Abortion and Stillbirth. JAMA. 2016; 315(1):58-67. doi:10.1001/jama.2015.17844.
3. The Malaysian National ADR Database, NPRA [Accessed August 2017].

Regulatory Matters

Tramadol: Restricted Use in Children and Warnings of Use in Pregnant and Breastfeeding Women

by Wan Noor Ardila Wan Abhar

Tramadol is an analgesic with opioid effects that is approved for the management of moderate pain. However, there is currently no available evidence for its comparative effectiveness and safety in children. Additionally, tramadol is not licensed for paediatric use in several countries like in Europe and Australia.

Background of the safety issue

NPRA has received information from the United States Food and Drug Administration (U.S. FDA) regarding the risk of slowed or difficult breathing and death that is associated with tramadol use, which appears to be a greater risk in children aged under 12 years. Based on the safety review, U.S. FDA has identified **nine cases of serious breathing problems**, including **three deaths with the use of tramadol in children younger than 18 years of age**. The U.S. FDA has currently contraindicated the use of tramadol in children aged under 12 years, and children below 18 years who have had a tonsillectomy and/or adenoidectomy, as well as recommending that tramadol should not be used in breastfeeding mothers due to possible harm to their infants.

In view of all collectible findings, U.S. FDA is adding new contraindications and warnings regarding this risk to the product information of medicines containing tramadol.

Registered Products in Malaysia

There are currently 37 products containing tramadol registered with the Drug Control Authority (DCA) as a single active ingredient (36 products) and in combination with paracetamol (1 product).

Local ADR Reports

Since year 2000, the NPRA has received 1,106 ADR reports with 1,884 adverse events related to the use of tramadol. The most commonly reported adverse events are vomiting, dizziness, nausea and pruritus. Adverse events related to the System Organ Class Respiratory and Mediastinal Disorders include dyspnoea, apnoea and respiratory distress. Currently, there are no local reports of respiratory depression associated with tramadol.

Regulatory Action

NPRA has completed the review of this safety issue and a directive [*Ref: Bil (25) dlm. BPFK/PPP/07/25 Jld. 1*] was issued for the package inserts of all registered products containing tramadol to be updated with the new age restriction in children and standardised safety information to warn against the use of tramadol in pregnant and lactating women.

Advice to Healthcare Professionals

- Tramadol is now **not approved** for use in patients below 12 years old.
- Tramadol is now **contraindicated** in:
  - Children younger than 18 years old to treat pain after surgery to remove the tonsils and/or adenoids.
  - Adolescents between 12 and 18 years who are obese or have conditions such as obstructive sleep apnea, which may increase the risk of serious breathing problems.
- Tramadol is **not recommended** for use in pregnant women and breastfeeding women. However, discontinuation of breastfeeding is generally not necessary following a single dose of tramadol.
- Report any adverse reactions suspected to be related to tramadol to the NPRA.

References

1. WHO (2012). WHO Guidelines on the Pharmacological Treatment of Persisting Pain in Children with Medical Illnesses.
2. U.S. FDA (2017). Drug Safety Communication: Restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against use in breastfeeding.
3. The Malaysian National ADR Database, NPRA [Accessed June 2017].

Regulatory Matters

Metformin: Use in Patients with Moderately Reduced Kidney Function

by Ng Chiew Seng

Background of the safety issue

As a first-line therapy for type 2 diabetes mellitus, metformin is one of the most commonly prescribed drugs worldwide. It is a biguanide agent which lowers both basal and postprandial plasma glucose. Metformin inhibits hepatic glucose production, reduces absorption of intestinal glucose, and improves glucose uptake and utilisation[1].

Metformin may increase the risk of a rare but serious complication called **lactic acidosis**, which occurs when naturally-produced lactic acid builds up in the blood faster than it can be removed. Currently, the product information states that metformin must not be used in patients with glomerular filtration rate (GFR) less than 60 ml/min because these patients are considered to be at a higher risk of developing lactic acidosis as their kidneys do not remove metformin efficiently enough.

The European Medicines Agency (EMA) reviewed the scientific literature, clinical data, epidemiological studies and clinical guidelines from medical bodies, concluding that the large patient population with moderately reduced kidney function can benefit from use of metformin. The dose of metformin should be adapted to the patient's kidney function. The use of metformin is still contraindicated in patients with severely reduced kidney function (GFR less than 30 ml/min)[2].

Registered Products in Malaysia

In Malaysia, there are currently 99 products containing metformin (either as single-ingredient products or in combination with other medicines) registered with the Drug Control Authority (DCA).

Local Scenario

NPRA has received 1,894 reports with 3,290 adverse events suspected to be related to metformin-containing products. Majority of the adverse events (1,347, 41%) involved gastrointestinal disorders such as diarrhoea, nausea and vomiting. To date, NPRA has received **40 reports of lactic acidosis**, **15 of which involved a fatal outcome**. Almost half of the total reports (19, 48%) involved **elderly** patients[3].

Regulatory Action

NPRA has reviewed this safety issue and a directive [*Ref: Bil (30) dlm. BPFK/PPP/07/25 Jld. 1*] was issued for all local package inserts and patient information leaflets of metformin-containing products to be updated with information on the use in patients with moderately reduced kidney function and a boxed warning on lactic acidosis.

The current Clinical Practice Guidelines: Management of Type 2 Diabetes Mellitus (5th edition, December 2015) already mentions that metformin can be used for patients with GFR <60 ml/min and is only contraindicated in chronic kidney disease stage 4 and 5 patients with GFR <30 ml/min[4].

Advice to Healthcare Professionals

- Metformin can now be used in patients with moderately reduced kidney function (GFR = 30-59 ml/min). However, use in patients with GFR<30 ml/min is still contraindicated.
- GFR should be assessed before initiation of treatment and at least annually thereafter.
- Reduced doses should be considered for patients with moderate reduction of kidney function according to **dosage recommendations** provided in the updated product information.
- Risk factors for lactic acidosis should be reviewed prior to and during treatment with metformin.
- Please report any adverse reactions suspected to be related to metformin to the NPRA.

References

1. Dumitrescu, R. *et al.* (2015). Metformin-Clinical Pharmacology in PCOs. J Med Life 8(2): 187-192.
2. European Medicines Agency (2016). Use of Metformin to Treat Diabetes Now Expanded to Patients with Moderately Reduced Kidney Function.
3. The Malaysian National ADR database, NPRA [Accessed: December 2017].
4. Clinical Practice Guidelines: Management of Type 2 Diabetes Mellitus (5th edition, December 2015).

Regulatory Matters

Metronidazole: Risk of Hepatotoxicity in Patients with Cockayne Syndrome

by Ng Chiew Seng

Background of the safety issue

Metronidazole is a synthetic nitroimidazole derivative. Metronidazole for systemic use is indicated for the treatment of anaerobic infections as well as protozoan infections such as amoebiasis (intestinal or hepatic), urogenital trichomoniasis, *Gardnerella vaginalis* infections and giardiasis[1].

Cockayne syndrome (CS) is a rare genetic disorder characterised by small stature, intellectual impairment, and accelerated pathologic aging[2]. The pathogenesis of CS is closely related to mutations in the ERCC6 (CSB) or ERCC8 (CSA) genes, which are involved in DNA repair.

Having considered the available evidence on the association between hepatotoxicity and metronidazole exposure in patients with CS, the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) agreed that the product information of metronidazole-containing medicinal products (except for external use on the skin) should be updated with warnings on the risk of hepatotoxicity[4].

Through the Cockayne Syndrome Natural History Study, eight (8) cases of acute hepatic failure after metronidazole administration were identified (8% of cohort), of which three (3) were fatal. The interval between initial administration and death was 6 to 11 days[2].

Registered Products in Malaysia

In Malaysia, there are currently 30 products containing metronidazole (excluding products for external use) registered with the Drug Control Authority (DCA).

Local ADR Reports

NPRA has received 521 reports with 965 adverse events suspected to be related to metronidazole-containing products. Majority of the adverse events (517, 54%) involved skin disorders, such as pruritus, urticaria and maculopapular rash. To date, NPRA has received six (6) reports of elevated liver enzymes post-metronidazole administration but it was not stated whether these patients had CS[5].

Regulatory Action

NPRA has reviewed this safety issue and a directive [*Ref: Bil (23) dlm. BPFK/PPP/07/25 Jld. 1*], was issued for all local package inserts and patient information leaflets of metronidazole-containing products to be updated with information on the risk of hepatotoxicity among CS patients.

Advice to Healthcare Professionals

- Cases of severe hepatotoxicity/acute hepatic failure in patients with Cockayne syndrome, including cases with very rapid onset and a fatal outcome, have been reported with products containing metronidazole for systemic use.
- In this population, metronidazole should therefore be used after careful benefit-risk assessment and only if **no alternative treatment** is available.
- Liver function tests must be performed just prior to the start of therapy, throughout and after end of treatment until liver function is within normal range, or until the baseline values are reached.
- If the liver function tests become markedly elevated during treatment, the drug should be discontinued.
- Patients with Cockayne syndrome should be advised to immediately report any symptoms of potential liver injury to their doctor and stop taking metronidazole.
- Please report any adverse reactions suspected to be related to metronidazole to the NPRA.

References

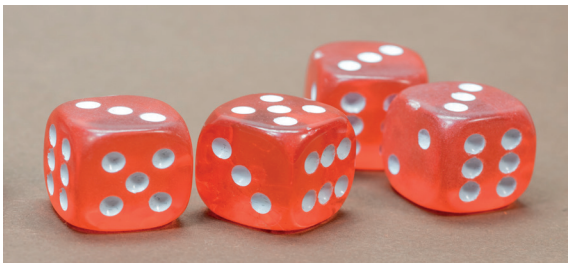
1. Swissmedic (2017). Vigilance-News Edition 18.
2. Wilson, B. T. *et al.* (2015). Metronidazole Toxicity in Cockayne Syndrome: A Case Series. Pediatrics 136(3): 706-708.
3. Kubota, M. *et al.* (2015). Nationwide Survey of Cockayne Syndrome in Japan: Incidence, Clinical Course and Prognosis. Pediatrics International 57: 339-347.
4. European Medicine Agency (2016). PRAC recommendations on signals adopted at the PRAC meeting of 26-29 September 2016.
5. The Malaysian National ADR database, NPRA [Accessed: December 2017]

Regulatory Matters

Aripiprazole: Risk of Pathological Gambling and Impulse-Control Problems

by Rema Panickar

Aripiprazole is an atypical antipsychotic which partially blocks the activity of dopamine receptors in the brain. It is indicated for the treatment of schizophrenia and for maintenance of clinical improvement, as well as treatment of acute manic episodes associated with Bipolar 1 Disorder.



Background of the safety issue

NPRA received information that both the United States Food and Drug Administration (U.S. FDA)[1] and the Therapeutic Goods Administration (TGA)[2] Australia, had reviewed cases of **impulse-control problems** suspected to be related to aripiprazole. These included reports of new or increased gambling urges, increased sexual urges, compulsive spending, and binge or compulsive eating.

While impulse-control symptoms can be associated with the patient's underlying disorder, in many of the cases, symptoms were reported to have stopped when the dose was reduced or the medication was discontinued.

The product information for aripiprazole-containing products has been updated with additional information on impulse-control disorders.

Registered Products in Malaysia

There are currently five (5) products containing aripiprazole registered with the Drug Control Authority (DCA).

Local ADR Reports

The NPRA has received 65 ADR reports with 111 adverse events suspected to be related to the use of aripiprazole. The most commonly reported adverse events are akathisia, restlessness, headache and somnolence.

Currently, the NPRA has not received any local reports related to gambling disorder/pathological gambling and impulse-control problems. A search of the WHO international database revealed 42,638 reports suspected to be related to aripiprazole received globally since the year 1997. Of these, 11,402 reports involved psychiatric disorders including gambling disorder, binge eating, compulsive shopping and libido increased/ hypersexuality.

Regulatory Action

NPRA has completed the review of this safety issue and a directive [*Ref: Bil (27) dlm. BPFK/PPP/07/25 Jld. 1*] was issued for the package inserts of all registered products containing aripiprazole to be updated with safety information on the risk of pathological gambling and impulse control problems.

Advice to Healthcare Professionals

- Rare but serious cases of impulse-control problems, including pathological gambling, increased sexual urges, binge eating, and compulsive shopping have been reported in patients treated with aripiprazole.
- Patients and caregivers should specifically be asked about the development of new or increasing compulsive behaviour, as they may not recognise these as abnormal.
- Patients should not suddenly stop taking aripiprazole without first talking to their healthcare professional.
- Consider dose reduction or stopping aripiprazole if a patient develops such urges during treatment.
- Please report any adverse reactions suspected to be related to aripiprazole to the NPRA.

References

1. U. S. FDA (2016). Drug Safety Communication: FDA warns about new impulse-control problems associated with mental health drug aripiprazole (Abilify, Abilify Maintena, Aristada).
2. Therapeutic Goods Administration (2017). Aripiprazole and impulse control disorders. Medicines Safety Update, Volume 8, Number 1.
3. The Malaysian National ADR Database, NPRA [Accessed June 2017].

ADR Reporting

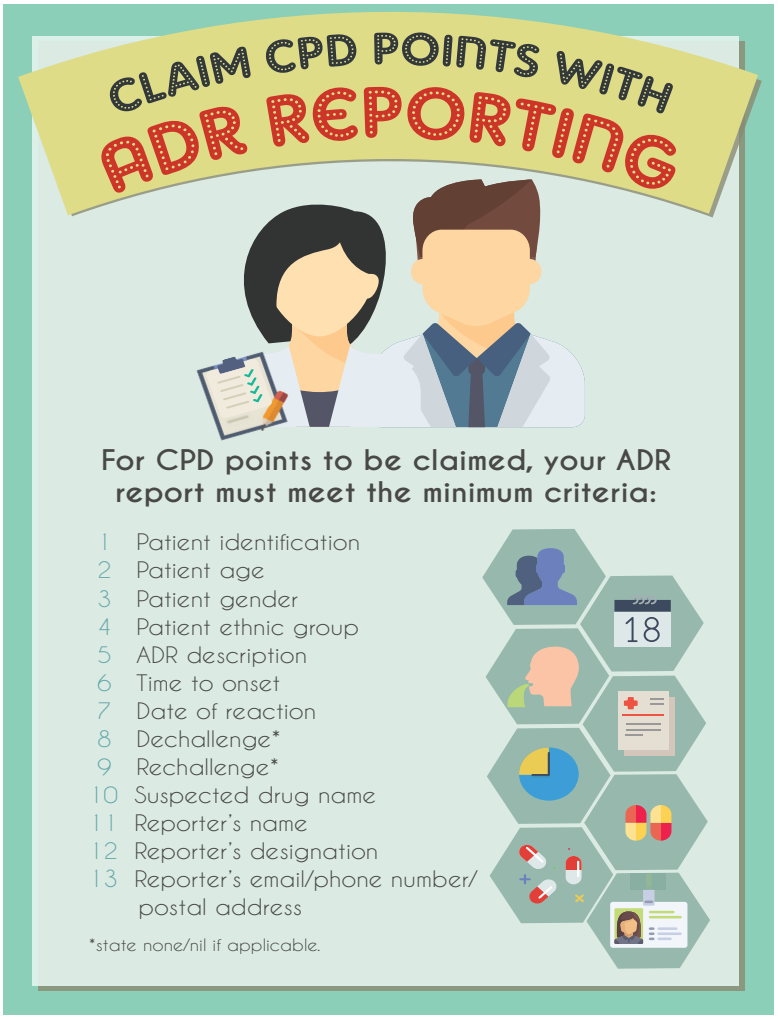
CPD Points for Quality ADR Reporting

In 2014, only three (3) ADR reports were received from community pharmacists, making up 0.02% of the total 13,001 reports received. The number of reports received from private hospitals was also low.

Since January 2016, pharmacists are eligible to claim Continuing Professional Development (CPD) points for the submission of quality ADR reports. The Pharmacy Board of Malaysia has agreed to award one (1) CPD point under category A4 for every ADR report submitted to the NPRA which **fulfils the mandatory criteria** (subject to a maximum of 10 points per year) as stated in the circulars [Ref: KKM-55/BPF/101/001/01 JLD 29 (20) and KKM.600-16/1/6(57)].

Since then, a total of 45 ADR reports were received from private sector pharmacists in 2016, of which 26 fulfilled the criteria for CPD point claim. In 2017, there was a slight increase of reports received, with a total of 52 ADR reports received which fulfilled the criteria for CPD point.

It is hoped that the number of quality ADR reports received will continue to increase, especially reports from the private sector. This will ensure the Malaysian ADR database contains comprehensive data to allow prompt detection of any safety issues.



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 and health supplements.

To report adverse drug reaction:

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 hard copy forms may be submitted via post, email or fax at:

The Pharmacovigilance Section,
National Pharmaceutical Regulatory Agency (NPRA),
Ministry of Health, Malaysia.
Lot 36, Jalan Universiti,
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*To join the **NPRA Safety Information Mailing List**, please send an email with your details to fv@npra.gov.my*

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