

MADRAC *Newsletter*

For healthcare professionals only

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Features

Recent Safety Issues with Fluoroquinolones

by Wan Noor Ardila Wan Abhar

Background

Fluoroquinolones are a class of antibacterial drugs that exhibit concentration-dependent bactericidal activity through the rapid inhibition of DNA gyrase and topoisomerase¹, enzymes that are essential for bacterial DNA replication. Due to their broad spectrum of activity and commendable potency, fluoroquinolones have a wide range of clinical indications for both gram-positive and gram-negative infections².

There are currently six different fluoroquinolones registered in Malaysia: ofloxacin, ciprofloxacin, levofloxacin, moxifloxacin, gemifloxacin and gatifloxacin. Since 2000, NPRA has received **1,160 ADR reports** with **3,024 adverse events** related to fluoroquinolones. The most commonly reported adverse events were pruritus (374, 12.4%), rash (202, 6.7%), maculo-papular rash (116, 3.8%) and urticaria (116, 3.8%).

In this article, NPRA looks at two (2) safety issues that have arisen, which are related to the use of fluoroquinolones: risk of retinal detachment, and the persistent and disabling side effects associated with fluoroquinolone use. Both safety issues have been evaluated by the European Medicines Agency (EMA) and United States Food and Drug Administration (US FDA) respectively. At present, NPRA is reviewing these issues. As the safety issues are still under evaluation, NPRA would like to urge healthcare professionals to monitor patients for the adverse events mentioned and report any cases to NPRA.

Recent Safety Issues

1 Risk of retinal detachment

Retinal detachment is a painless separation of the retina from the layer of support tissue and blood vessels at the back of the eye³. It is a serious medical emergency that may lead to irreversible vision loss⁴. Over the past decade, fluoroquinolones have been associated with the risk of retinal detachment. The mechanism of this event was thought to be due to the destructive effect of the drug on the connective tissue and collagen fibers, which make up the structure and integrity of the vitreous body⁵.

EMA has investigated the association between fluoroquinolone intake and occurrence of retinal detachment in several epidemiological studies. It was found that two studies (Etminan *et al.* 2012, Kuo *et al.* 2014) showed a statistically significant increased risk of developing retinal detachment with the use of oral fluoroquinolones⁶. Review of non-clinical data also identified a few cases of retinal detachment with fluoroquinolones and suggested a possible ophthalmological toxicity of fluoroquinolones. Although the causal relationship between fluoroquinolone intake and retinal detachment can neither be established nor firmly excluded at the time of the review, EMA considered that all product information for fluoroquinolone-containing products should be updated with a warning on this risk, as



retinal detachment is a serious medical emergency and requires urgent medical intervention should it ever occur.

At the time of this publication, no ADR report on retinal detachment with fluoroquinolone use has been received by NPRA. The adverse events related to eye disorders which have been reported include **eye swelling (15)**, **eye pain (4)**, **blurred vision (2)** and **decreased vision (1)**.

Local Case Report: Blurred vision

One case of **blurred vision** was reported in a 44-year-old female patient who was prescribed ciprofloxacin tablet 250 mg twice daily for urinary tract infection (UTI). Two days after drug initiation, the patient developed blurred vision and asthenia. The patient was reported to be taking two concomitant drugs for UTI treatment, and had underlying asthma, gastritis and gout.

Local Case Report: Decreased vision

One case of **decreased vision** was reported in a 47-year-old diabetic patient who was prescribed with levofloxacin, along with cycloserine, kanamycin, ethionamide and pyrazinamide as a second-line therapy for multiple-resistant tuberculosis infection. After 3 months of second-line tuberculosis therapy, patient developed drug-associated side effects that included decreased vision, hearing loss, tinnitus, and giddiness. Kanamycin was stopped because of its ototoxic effects. After another 2 months of treatment, patient continued to experience nausea, vomiting, arthralgia and intermittent loss of appetite. Treatment was halted when susceptibility testing of the *Mycobacterium tuberculosis* isolate showed that it was resistant to all the aminoglycoside and fluoroquinolone antibiotics tested. Following treatment failure with primary and secondary antituberculosis drugs due to non-compliance to pharmacotherapy and uncontrolled diabetes, patient was diagnosed with extensively drug-resistant tuberculosis (XDR-TB) infection. No information was given on whether or not the adverse events subsided upon drug withdrawal. While the role of the drugs cannot be ruled-out for the events, their role cannot be assessed in isolation due to co-suspect drugs.

2 Persistence of serious side effects mainly affecting muscles, joints and the nervous system

The United States Food and Drug Administration (US FDA) has completed a review on the link between the use of systemic fluoroquinolones and persistence of serious side effects that mainly affect muscles, joints and the central nervous system⁷. The serious side effects identified in the review are related to the:

- (i) Musculoskeletal and peripheral nervous system, such as **tendonitis, tendon rupture, muscle weakness, muscle pain, joint pain, joint swelling, numbness or tingling or pricking sensation in arms or legs;**
- (ii) Central nervous system such as **anxiety, depression, hallucinations, confusion, and suicidal thoughts.**
- (iii) Other body systems, such as **skin rash, severe diarrhoea, abnormal and rapid or strong heartbeat, and worsening of myasthenia gravis.**

The review concluded that these reactions may occur together in the same patient, with **onsets within hours to weeks** after fluoroquinolone treatment initiation. The reactions are also considered disabling and potentially permanent to the patient.

NPRA has received reports related to the musculoskeletal disorders with fluoroquinolone use, such as cases of **tendonitis (3)**, **muscle weakness (1)**, **joint pain (1)**, and **joint stiffness (1)**.

Local Case Report: Tendonitis

One of the reports of **tendonitis** with fluoroquinolone use involved a 35-year-old female patient who was receiving levofloxacin 500 mg twice daily as a second-line treatment for *Helicobacter pylori* infection, along with amoxicillin 1 g twice daily and esomeprazole 40 mg twice daily. She was reported to experience Achilles tendonitis after 6 days of treatment, and recovered after levofloxacin was stopped. No medical history was provided in this report.



For adverse events related to the central nervous system disorders, cases of **hallucination (4)**, **anxiety (1)**, **confusional state (1)**, **depression (1)** and **suicidal ideation (1)** have been reported with fluoroquinolone use.

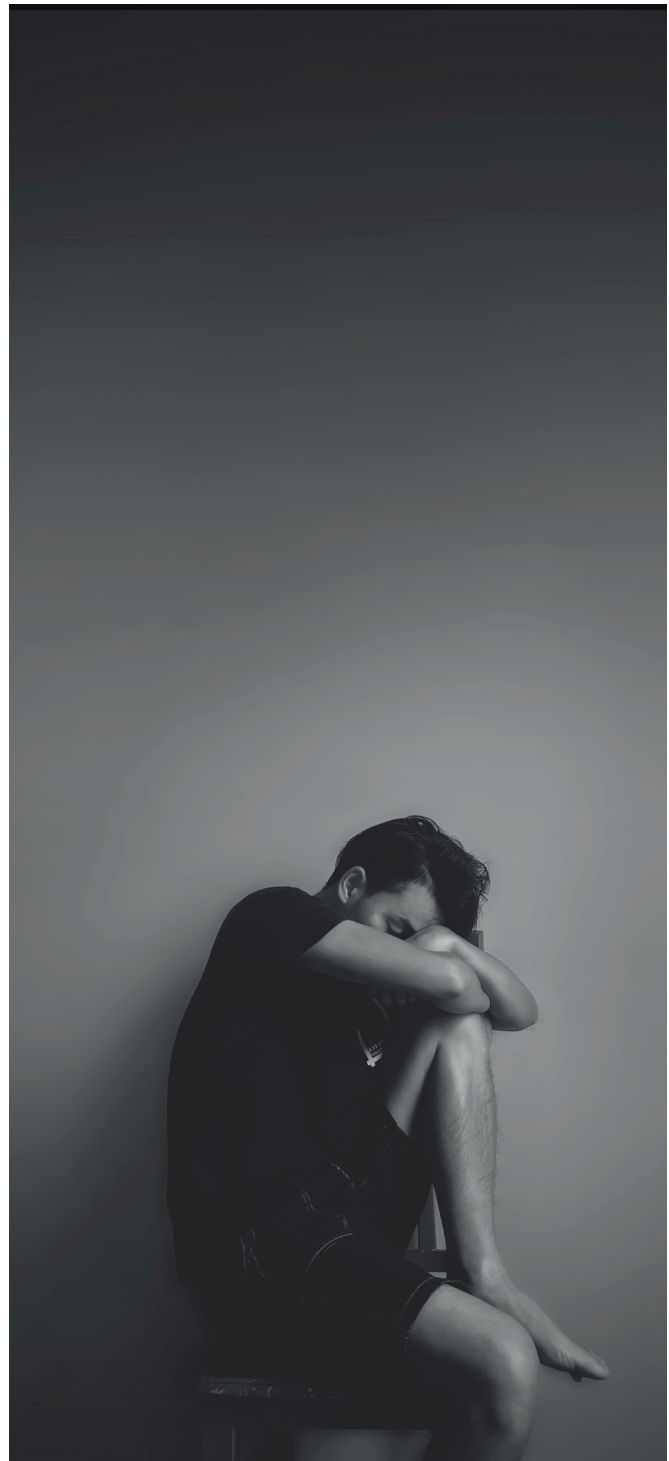
Local Case Report: Depression

There was one case that reported **depression** and **suicidal ideation** with the use of moxifloxacin in a 60-year-old female patient. The patient, whose medical illness and concomitant drugs were not provided in this report, was given moxifloxacin tablet 400 mg for an unknown indication. Patient began to develop depression and subsequently suicidal ideation. When moxifloxacin was withdrawn, the depression was reported to be resolving.

All the case reports mentioned above were given the causality possibly-related (C3) due to the presence of concomitant medication or underlying medical conditions.

Advice to Healthcare Professionals

- Upon initiating fluoroquinolones, patients should be advised to immediately consult their doctor if vision becomes impaired or any effects on the eyes are experienced.
- Disabling and potentially irreversible serious adverse reactions including tendonitis and tendon rupture, peripheral neuropathies, and central nervous system effects have been associated with fluoroquinolone use, and may occur together in the same patient.
- **Fluoroquinolones should be used with caution in elderly patients.** Majority of fluoroquinolones, such as ofloxacin, levofloxacin and gatifloxacin are excreted mainly by the kidney (moxifloxacin is excreted hepatically). As elderly patients are more likely to have decreased renal function, the risk of fluoroquinolone-associated adverse reactions may be greater in this patient group.
- Inform patient to stop taking the fluoroquinolone and seek medical attention if they experience an adverse reaction.
- Report to NPRA if any adverse drug reaction occurs with fluoroquinolone use.



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1. Oliphant and Green (2002). Quinolones: A Comprehensive Review. American Family Physician; Clinical Pharmacology, Volume 65, Number 3, p455-464.
2. National Antibiotic Guidelines 2nd Edition (2014). Ministry of Health, Malaysia.
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6. EMA (2014). PRAC recommendations on signal adopted at the PRAC meeting of 10-13 June 2014. EMA/PRAC/337405/2014.
7. US FDA (2017). FDA Drug Safety Communication: FDA updates warnings for oral and injectable fluoroquinolone antibiotics due to disabling side effects.
8. The Malaysian National ADR Database, NPRA [Accessed: April 2018].

Articles based on Case Reports

Simvastatin: Reminder on the Risk of Cognitive Impairment

by Bong Wan Kwin

Case Report 1

A 42-year-old female patient developed **forgetfulness** after 4 months of taking simvastatin for dyslipidaemia. Following the adverse event, the drug was discontinued and changed to fenofibrate. The patient was reported to have recovered from the adverse event. As the patient had underlying rheumatoid arthritis and was on other concomitant medications which may have contributed to the adverse event, this case was assigned causality C3 (possibly-related to the drug).

Case Report 2

Another similar case was reported in 2017, involving a 53-year-old female diabetic patient who experienced **forgetfulness** and **confusion** after taking simvastatin for 2 months. Simvastatin was then discontinued and changed to atorvastatin, however, the outcome of the event was not reported. Considering that the patient was on other concomitant medications that may have possibly contributed to the adverse events, the causality given for this case was C3 (possibly-related to the drug).



Discussion

Simvastatin belongs to a class of anti-hyperlipidaemic drugs called HMG-CoA reductase inhibitors, which act by inhibiting the rate-limiting enzyme in hepatic cholesterol synthesis¹. There are currently **30 products** containing simvastatin registered with the Drug Control Authority (DCA) in Malaysia. It is approved for the treatment of dyslipidaemia, as well as for primary and secondary prevention of heart attack and stroke.

Statins are generally well-tolerated and have minimal serious adverse events, such as hepatitis and rhabdomyolysis. From year 2000 until December 2017, NPRA has received **2,105 ADR reports** with **3,307 adverse events** suspected to be related to simvastatin. The most commonly reported adverse events were dizziness (268, 8.1%), pruritus (247, 7.5%), headache (185, 5.6%), myalgia (151, 4.6%) and rash (133, 4.0%).

In recent years, statins have been linked to several different safety issues including muscle-related adverse events, risk of hyperglycaemia, and cognitive impairment². The summary of safety concerns linked to statins has been discussed in [MADRAC Newsletter August 2014](#), with directives issued by the DCA in September 2014, requiring the package inserts of all products containing statins to be updated with information on these risks [[Ref: \(14\) dlm.BPFK/PPP/07/25](#)].

Cases of possible statin-related cognitive impairment such as memory loss, forgetfulness, amnesia, memory impairment and confusion have been reported in post-marketing experience worldwide. The reports were largely non-serious and reversible upon statin discontinuation⁴. It was suggested that the

statin-associated cognitive impairment may have been linked to the pharmacological properties of the statin. Lipophilic statins such as atorvastatin and simvastatin show an increased penetration of the drug across the blood-brain barrier, as compared to the hydrophilic statins (e.g. pravastatin and rosuvastatin)⁵. Nevertheless, the cardiovascular reduction benefits seen with statins generally outweigh the risk of developing statin-associated adverse events¹.

Advice to Healthcare Professionals

- Monitor patients for symptoms of cognitive impairment (e.g. memory loss, forgetfulness, amnesia, memory impairment, confusion).
- Counsel patients to recognise the signs and symptoms of cognitive impairment and advise them to seek medical attention promptly if they experience any of the symptoms.
- Report any adverse events suspected to be associated with the use of statins to the NPRA.

References

1. Ministry of Health Malaysia (2017). Malaysian Clinical Practice Guidelines on The Management of Dyslipidaemia.
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3. MADRAC Newsletter August 2014.
4. Carlos H Rojas-Fernandez & Jean-Christy F Cameron (2012). Is Statin-associated Cognitive Impairment Clinically Relevant? *The Annals of Pharmacotherapy* 46(4):549-557.
5. The Malaysian Adverse Drug Reaction Database, NPRA [Accessed: March 2018]

Articles based on Case Reports

Dipeptidyl Peptidase-4 Inhibitors: Reminder on the Risk of Pancreatitis

by Syifa' Izzati Mohd. Zainul

Case Report

One **pancreatitis** case involved a 73-year-old male, who complained of having abdominal pain for one day prior to hospital admission. The pain initially started around the epigastric region and then progressed to generalised abdominal pain. He also complained of vomiting more than 10 times. The patient was later diagnosed as having acute pancreatitis (Ranson score: 3) possibly due to saxagliptin and gradually recovered after the drug was stopped. This case was given causality C3 (possibly-related to drug) as the patient was also on multiple concomitant medications.

Discussion

Dipeptidyl peptidase-4 (DPP-4) inhibitors, or most commonly known as the gliptins, are indicated for improving glycaemic control in adults with type 2 diabetes mellitus, together with lifestyle changes. There are currently **32 products** containing DPP-4 inhibitors registered in Malaysia, as single ingredient or in combination with other drugs.

NPRA has received a total of **383 ADR reports**, with **593 adverse events**, suspected to be related to the use of DPP-4 inhibitors. Commonly reported adverse events were rash (30), nausea (29), diarrhoea (25), pruritus (22), and vomiting (22).

Use of DPP-4 inhibitors has been associated with a risk of developing pancreatitis. This risk has already been documented as a possible adverse reaction in the local package insert for all DPP-4 inhibitors registered in Malaysia.

Locally, including the case report above, **six (6) cases of pancreatitis** have been reported, which involved sitagliptin and saxagliptin.

As of April 2018, the WHO global ADR database (VigiBase)* contains 3,363 reports of pancreatitis, 1,217 reports of acute pancreatitis and 145 reports of chronic pancreatitis, which are suspected to be caused by DPP-4 inhibitors.

*DISCLAIMER

This information comes from a variety of sources, and the likelihood that the suspected adverse reaction is drug-related is not the same in all cases. This information does not represent the opinion of WHO.

References

1. Ministry of Health Malaysia (2015). Clinical Practice Guideline on the Management of Type 2 Diabetes Mellitus.
2. MADRAC Newsletter Volume 22, Issue 01/2017.
3. The Malaysian Adverse Drug Reaction Database, NPRA [Accessed: April 2018]



Advice to Healthcare Professionals

- Upon initiation of DPP-4 inhibitors, patients should be informed on the characteristic symptoms of acute pancreatitis: persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting. Encourage patients to inform their healthcare professionals immediately if they have such symptoms.
- Whenever pancreatitis is suspected, DPP-4 inhibitors should be discontinued and should not be restarted if the diagnosis is confirmed.
- It is unknown whether patients with a history of pancreatitis are at increased risk for developing pancreatitis, but extra caution should be exercised nonetheless.
- Please report any ADRs suspected to be related to the use of DPP-4 inhibitors to the NPRA.

Articles based on Case Reports

Povidone-iodine Gargle: Risk of Hypothyroidism

by *Wo Wee Kee*

Case Report

The NPRA has received a report of reversible **hypothyroidism** suspected to be related to povidone-iodine gargle use in a 34-year-old male patient. This patient had been regularly using povidone-iodine gargle twice daily for 3 months before a blood test revealed an elevated thyroid-stimulating hormone (TSH) level of 10.015 $\mu\text{U/mL}$ (normal range 0.35- 5.5 $\mu\text{U/mL}$). Ultrasound examination revealed that the patient had multinodular goiter, and he was advised to stop using the gargle immediately. A repeat blood test 11 days later showed a reduced TSH level of 6.639 $\mu\text{U/mL}$. Patient was reported to be recovering from hypothyroidism at the time of reporting, and no rechallenge was performed.



Discussion

Povidone-iodine or polyvinylpyrrolidone iodine (PVP-I) is a broad spectrum microbicide¹. Free iodine is slowly released from the PVP-I complex in solution, killing cells through iodination of proteins and oxidation of membrane compounds. There are 34 products containing povidone-iodine registered for human use in Malaysia, of which **four (4) products** are indicated as **mouthwash/gargle/throat spray**. The remaining products are solutions, creams, ointments, paints and douches for topical use. Since year 2000, NPRA has received **21 ADR reports** suspected to be related to povidone-iodine use, with **35 adverse events**. The most commonly reported adverse events were dermatitis, application site reactions, and pruritus. There were **three (3) reports** involving the mouthwash/gargle/throat spray.

The routine use of povidone-iodine mouthwash has been linked to cases of iodine-induced hypothyroidism². Although most of the mouthwash would be spat out during gargling, a small proportion would be swallowed, hence its prolonged use may interfere with thyroid function tests, leading to diagnosis of goitre and hypothyroidism or hyperthyroidism. However the hypothyroidism/hyperthyroidism usually resolves spontaneously and rapidly following cessation of product use. The case mentioned above is the first report received by NPRA on products containing povidone-iodine causing hypothyroidism or any thyroid disorders.

A search of the WHO global ADR database (VigiBase)* revealed 21 cases of hypothyroidism reported, regardless of the route of administration of povidone-iodine.

*DISCLAIMER

This information comes from a variety of sources, and the likelihood that the suspected adverse reaction is drug-related is not the same in all cases. This information does not represent the opinion of WHO.

Advice to Healthcare Professionals

- Patients should be counselled not to use any mouthwash containing iodine for more than 14 days.
- Advise patients to stop using the product and seek prompt medical attention if symptoms of hypothyroidism or hyperthyroidism appear.
- Please report any adverse events suspected to be related to the use of povidone-iodine containing products to the NPRA.

References

1. Povidone iodine (OTC). Medscape: Drugs & Diseases.
2. Sato K, Ohmori T, *et al.* (2007). Povidone Iodine-Induced Overt Hypothyroidism in a Patient With Prolonged Habitual Gargling: Urinary Excretion of Iodine After Gargling in Normal Subjects. *The Japanese Society of Internal Medicine.* 46(7):391-5.
3. The Malaysian Adverse Drug Reaction Database, NPRA [Accessed: April 2018].

Articles based on Case Reports

Adulteration of Traditional Products with Corticosteroids: Risk of Psychiatric Disorders

by Nurul Aimi Mohd. Reduzan

Case Report 1

A 60-year-old male developed **abnormal behaviour** and **manic symptoms** after two weeks of consuming a traditional preparation named Skyline Al Taqwa Sakit Pinggang & Lutut* for polyarthralgia. The patient claimed to have experienced immediate pain relief after starting this traditional product. However, his family members noticed behavioural changes and took him to seek psychiatric treatment. Through detailed history-taking, the attending doctor suspected that the abnormal behaviour may be linked to use of the traditional product. The patient recovered fully once he stopped taking the product. The product was tested and found to contain undeclared dexamethasone.

Case Report 2

A 67-year-old male bought the traditional medicine, Pil Penawar Raja Saraf Original Pekisa*, from an agent in Sitiawan. He started taking the product in June 2015 for general health and vitality. After about a month of consuming the product, he started experiencing **personality changes** and became easily **irritated**. He also had **difficulty sleeping** at night. The patient was brought to a psychiatric clinic, diagnosed with **bipolar disorder**, and discharged with three antipsychotic medications. The traditional product was stopped. At the time of reporting, the patient had not fully recovered. The product was tested and found to be adulterated with dexamethasone.

Case Report 3

A 72-year-old male developed **manic disorder** after two weeks of taking two types of traditional products for treatment of numbness and pain. The products consumed were called Ratu Glowing Penawar Raja Saraf* and Herba Qaseh Serata Herbs*, both found to be adulterated with dexamethasone. Patient outcome was not yet known at the time of reporting.

*Note: Traditional products mentioned in this article are unregistered products.

Discussion

Psychiatric symptoms, especially **mania** are known but unpredictable side effects of corticosteroid use. The symptoms include **psychosis, depression, mania, bipolar disorder**, and also reactions such as **insomnia, anxiety** or **panic attacks**. Even though it is common, the mechanism by which corticosteroids cause these symptoms is still not fully understood and may be influenced by confounding factors and concurrent medications used.

The occurrence of psychiatric symptoms is of even greater concern in the case of adulterated traditional products as compared to prescription medication known to contain corticosteroids. Patients prescribed with corticosteroids would be given adequate counselling on the possible adverse effects, advised to seek



medical assistance when necessary, and closely monitored throughout the treatment. On the other hand, those who take traditional products usually do so without the knowledge of their healthcare professionals. Without proper counselling and monitoring, patients who develop psychiatric adverse events may not be managed appropriately. They may even be misdiagnosed with a psychiatric condition and treated long-term with antipsychotics, if their healthcare professional remains unaware of the traditional product use.

Corticosteroids are one of the most common adulterants among products tested in Malaysia, possibly due to the rapid onset of action to relieve symptoms. Therefore, people who consumed products adulterated with corticosteroids may mistakenly believe the product to be effective in relieving their pain or discomfort. However, the use of corticosteroids brings with it various possible adverse effects, especially when used long-term or stopped abruptly. While the [Pharmacy Enforcement Division](#) is constantly taking stern action against sellers and manufacturers of adulterated products, these products remain widely available as there is an apparent high demand for them.

Advice to Healthcare Professionals

- Keep in mind the possibility of psychiatric symptoms being induced by adulterated traditional products.
- Always ask patients if they are taking any traditional products, besides other concomitant medication.
- Any adverse events suspected to be associated with the use of traditional products should be reported to the NPRA.
- Please report any sale/distribution/manufacturing of unregistered traditional products to the nearest [Pharmacy Enforcement Division](#).

References

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2. Michael AC (2006). Corticosteroid-induced mania: Prepare for the unpredictable. *Current Psychiatry*. 5(6):43-50.
3. Miriam C., *et al.* (2013). Corticosteroid-related central nervous system side effects. *J Pharmacology Pharmacotherapy*. 4(Suppl1): S94-S98.
4. Waljee AK, *et al.* (2017). Short term use of oral corticosteroids and related harms among adults in the United States: population based cohort study. *BMJ* 357:j1415.

What's New?**List of Directives Related to Drug Safety Issues (January - April 2018)**

NPRA reviews and presents drug safety issues at MADRAC meetings 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 of all products containing the affected active ingredients are updated with the required safety information. The following are DCA directives issued between January to April 2018, which may be downloaded from the NPRA website.

	Active ingredient	Safety Issue	Date	Directive Reference number
1	Minocycline	Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)	27 February 2018	[Ref: (6) dlm.BPFK/PPP/07/25 Jilid 2]
2	Propofol and sodium valproate	Drug interaction causing increased blood levels of propofol	27 February 2018	[Ref: (7) dlm.BPFK/PPP/07/25 Jilid 2]
3	Amoxicillin	Severe Cutaneous Adverse Reactions (SCARs); Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)	27 February 2018	[Ref: (8) dlm.BPFK/PPP/07/25 Jilid 2]
4	Gabapentin	Respiratory depression	27 February 2018	[Ref: (9) dlm.BPFK/PPP/07/25 Jilid 2]
5	Mesalazine	Photosensitivity	18 April 2018	[Ref: (12) dlm.BPFK/PPP/07/25 Jilid 2]
6	Ethinylestradiol	Risk of increased levels of alanine transaminase (ALT)	18 April 2018	[Ref: (13) dlm.BPFK/PPP/07/25 Jilid 2]
7	Carbocisteine and acetylcysteine	Anaphylactic/ anaphylactoid reaction; Severe Cutaneous Adverse Reactions (SCARs)	18 April 2018	[Ref: (14) dlm.BPFK/PPP/07/25 Jilid 2]

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 np.ra.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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