National Pharmaceutical Regulatory Agency
Ministry of Health, Malaysia

# MADRAC Bulletin

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## In this Issue



*Features*

## Malaysian NPRA-Australian TGA Seminar on Safety Signal Management

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects of any other medicine/vaccine related problem [World Health Organisation (WHO), 1968]. Pharmacovigilance activities carried out by the National Pharmaceutical Regulatory Agency (NPRA) include adverse event (AE) collection and monitoring, safety signal detection, risk evaluation and management, and risk communication.

NPRA takes steps to continuously strengthen and refine the regulatory process through engagements and consultations with other regulatory agencies. In 2021-2022, NPRA has been involved in the Regulatory Strengthening Program conducted by the Australian Therapeutic Goods Administration (TGA), which include technical assistance and collaboration in pharmacovigilance.


A seminar on safety signal management was conducted on 30-31 March 2022 for all NPRA pharmacovigilance staff with speakers from both NPRA and TGA.

During the session, TGA shared their experiences in signal investigations, which include signal detection, signal prioritisation, and signal assessment for medicines and vaccines. NPRA's pharmacovigilance team also presented the signal management process currently in place at NPRA for TGA's input for further improvement in this newly initiated activity. Several ideas and ways to enhance local safety signal management were discussed.

Signal management is one of the key activities in pharmacovigilance. The signal management is a process of multiple activities (***Figure 1***) performed to determine whether there are new risks associated with an active substance or a medicinal class, or whether known risks have changed in frequency or severity.


*Figure 1: Signal management process in pharmacovigilance*

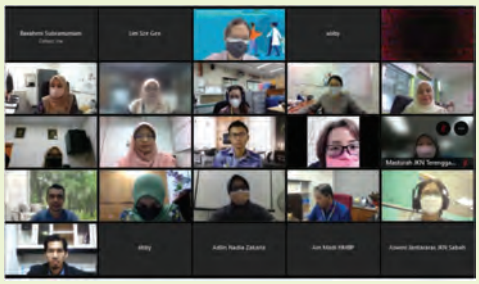
A discussion session on Effective Communication of Safety Risks was also held on 18 March 2022. TGA shared their experience on effective risk communication, particularly with regards to communicating information on COVID-19 vaccines safety, to the public.

## *Features*

# NPRA's Training Workshops on COVID-19 Vaccine AEFI Reporting, Case Investigation and Risk Communication

In the year 2022, the Pharmacovigilance Section of NPRA had successfully organised two (2) virtual training workshops related to the adverse events following immunisation (AEFIs) of COVID-19 vaccines.

In February 2022, a total of 90 medical doctors and pharmacists from various health facilities in the country attended the first training workshop to receive comprehensive training on how to improve COVID-19 vaccine-specific AEFI reporting and case investigation. The importance of effective risk communication and its impacts to public health were also discussed.



The second training workshop, which was held in April 2022, focused on death reports suspected to be COVID-19 vaccine-related. It was attended by a total of 284 physicians, pharmacists, and medical assistants from the Ministry of Health facilities around the country.

In this workshop, common misconceptions about AEFI investigation and causality assessments pertaining to death cases were clarified. The roles of forensic pathologists in suspected AEFI death cases investigation were also explained and emphasised. During the last session of the workshop, the participants were actively engaged in the case discussions requiring forensic assessments.

*Features*

# Summary Report on Adverse Events Following Immunisation of COVID-19 Vaccines in Malaysia #4

The NPRA monitors the safety of COVID-19 vaccines to ensure that they remain safe for use and the benefits of these vaccines continue to outweigh the risks in the Malaysian population. As part of continuous monitoring efforts, NPRA is publishing key findings of this safety monitoring.

The current summary report is based on the data up to 10 June 2022.

*Read the summary report here.*


Summary Report on Adverse Events Following Immunisation of COVID-19 Vaccines in Malaysia

Introduction

**13,778**

Minor AEFI responses per 1,000,000 doses

**371**

Overall AEFI reports per 1,000,000 doses

**93%**

Percentages of non-serious AEFI reports

**26**

Serious AEFI reports per 1,000,000 doses

Similar to global scenario, the vast majority (93%) of the reported AEFIs in Malaysia are non-serious. The most common reactions included injection site pain, headache, fatigue, muscle or join pain, lethargy and fever.

The rate of serious AEFIs reported via the NPRA Reporting System is small at 26 per 1,000,000 doses, most requiring short-term hospitalisation for observation and treatment.

Based on the current data, the benefit-to-risk-ratio of COVID-19 vaccines registered in Malaysia remains very favourable.

The NPRA encourages all healthcare professionals and patients to report any suspected AEFIs so that potential new risks can be identitied, and appropriate safety measures and regulatory actions can be taken to mitigate the risk

## *Articles Based on Case Reports*

# Iron Dextran: Risk of Seizures

*by Ng Wan Ning*

### *Case Report 1* [1]

A 29-year-old female patient with no history of seizures was prescribed iron dextran for anaemia in pregnancy. Fifteen (15) minutes after receiving an intravenous bolus test dose of iron dextran, the patient developed a **generalised tonic-clonic seizure** for two (2) minutes. The fits episode resolved spontaneously and the patient was hospitalised.

### *Case Report 2* [1]

A 34-year-old male patient with underlying ulcerative colitis was given iron dextran for iron deficiency anaemia. Following a 3-minute intravenous infusion of the iron dextran test dose, the patient experienced **up-rolling of eyeballs accompanied by tonic movements of bilateral upper and lower limbs** that lasted less than 10 seconds. The iron dextran intravenous infusion was stopped immediately following the event. The patient also complained of blurred vision and suprapubic pain that persisted for one (1) hour after the fitting ceased.

## Discussion

Iron dextran is an injectable medication generally indicated as replacement therapy for iron deficiency, when oral iron preparations cannot be used or when there is a clinical need to deliver iron rapidly to iron stores.[2] Following the intravenous administration, the iron (III)-hydroxide dextran complex is rapidly taken up by the cells of the reticuloendothelial system (RES), which split the complex into its components of iron and dextran. The iron is immediately bound to the available protein moieties to form hemosiderin or ferritin, or to a lesser extent, transferrin. This iron, which is regulated by the physiological control of iron balance, replenishes haemoglobin and depleted iron stores.[2-3]

Seizure has been documented as a rare (>1/10,000 - <1/1,000) adverse event of iron dextran.[2] Tonic-clonic seizure has also been reported with other intravenous irons, i.e., iron(III) isomaltoside 1,000, in a patient with no known predisposition to seizures in a randomised clinical study of inflammatory bowel disease (IBD) population. However, the mechanism behind these seizures remains unknown.[4-5] According to the available literature, there is no single mechanism that can explain all cases of drug-induced seizures. The majority are short-lived, self-limiting, and do not cause permanent sequeale. It is also possible that seizures associated with iron dextran may go unnoticed and under-reported. Nonetheless, recurrent or continuous seizures may cause irreversible neurological injury as well as other life-threatening complications such as hypoxia or pulmonary aspiration.[6-7]

In Malaysia, there is currently one (1) registered pharmaceutical product that contains iron dextran in an injectable formulation.[8] To date, NPRA has received 967 ADR reports with 2,152 adverse events associated with iron dextran use. The most commonly involved system organ classes (SOC) were skin and subcutaneous tissue disorders (480), respiratory, thoracic and mediastinal disorders (436), and general disorders and administration site conditions (338), with shortness of breath, pruritus, and dizziness being the most frequently reported adverse events.[1]

At the time of writing, there were **nine (9) local cases** involving eight (8) female patients and one (1) male patient between 29-42 years old, including the two (2) cases described above. The reported adverse events were generalised tonic-clonic seizure (2), tonic-clonic seizure (1), seizure (5), tonic clonic movements (1), and eyes gaze upward (1), with time-to-onset ranging from seconds to 15 minutes. All patients were reported to have recovered from the adverse events following drug withdrawal.[1] As of May 2022, a search of the World Health Organisation (WHO) database identified 110 cases reporting seizures of all subtypes under the MedDRA High-Level Group Term (HLGT), including 13 cases of generalised tonic-clonic seizures, suspected to be related to iron dextran use.[9*]

*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

1. Be aware of the possible risk of seizures in patients receiving iron dextran, particularly during the initial administration and in high-risk patients.
2. Seizures associated with iron dextran use, which can be transient in nature, may go unnoticed.
3. Should seizures occur, it is important to provide prompt treatment including good supportive care and administration of optimise anticonvulsant drug therapy.
4. Report all suspected adverse events associated with iron dextran use to the NPRA.

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*Articles Based on Case Reports*

# Hydroxyurea for Myeloproliferative Disorder: Risk of Cutaneous Vasculitis and Gangrene

*By Farah Faridah binti Jamaludin*

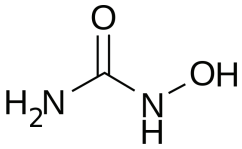
### *Case Report 1* [1]

A 69-year-old male patient was initiated on oral hydroxyurea 1g twice daily for thrombocytosis meanwhile to confirm the diagnosis of myeloproliferative disorder. Two (2) days later, the patient complained of pain and swelling in the right hip. Physical examination revealed tenderness from above the knee to the proximal thigh and bruises on the lateral thigh. The patient was diagnosed with **possible gangrene/cutaneous vasculitis** secondary to hydroxyurea. After the suspected medication was withheld, the cutaneous reaction subsided and the patient was continuously monitored in the ward.

### *Case Report 2* [1]

A 68-year-old male patient with underlying Janus kinase (JAK) 2 mutation-negative essential thrombocythaemia was started on oral hydroxyurea 1g daily. One (1) week after initiating hydroxyurea, the patient developed **Fournier's gangrene of the scrotum** and was admitted to the hospital for wound debridement. Hydroxyurea was withdrawn and switched to anagrelide. The patient had yet to recover from the adverse events at the time of reporting.

## Discussion




Hydroxyurea, also known as hydroxycarbamide, is an antineoplastic agent indicated for the treatment of melanoma, resistant chronic myelocytic leukaemia, and recurrent, metastatic, or inoperable carcinoma of the ovary.[2] It may also be used concomitantly with irradiation therapy for the local control of primary squamous cell carcinomas of the head and neck (excluding the lip).[2] The precise mechanism of action has not been clearly defined, but various studies support the hypothesis that hydroxyurea inhibits DNA synthesis, by acting as a ribonucleotide reductase inhibitor, without interfering with RNA or protein synthesis.[2-4]

Multiple cutaneous adverse events, such as skin ulceration, gangrene, hyperpigmentation, skin and nail atrophy, xerosis, alopecia, and malignant lesions, have emerged as a result of the widespread use of hydroxyurea. During therapy with hydroxyurea, cutaneous vasculitic toxicities, including vasculitic ulcerations and gangrene, have been reported in patients with myeloproliferative disorders.[4-6] While the pathogenesis of hydroxyurea-induced cutaneous vasculitic toxicities and gangrene remains poorly understood, it is hypothesised to be multifactorial.[5-6]

Hydroxyurea is known to induce macrocytosis, which causes enlarged red blood cells to circulate poorly across the capillary network and impairs microcirculatory blood flow. Owing to its cytostatic nature, hydroxyurea may also induce cumulative toxicity in the basal layer of the epidermis, which can lead to cutaneous atrophy and impaired wound healing with dermal fibrosis and occasional fibrinoid thrombi.[5-8] On top of that, patients affected by myeloproliferative disorders are usually old, where vascular insufficiency is common and likely contributes to ischaemia and delayed wound healing.[5-6] Traumas or repeated mechanical injury in the setting of impaired skin barriers may also act as triggers for ulcerations and gangrene.[6,8]

Fournier's gangrene is a specific type of necrotising fasciitis. It is a rare but severe and potentially life-threatening soft tissue infection that affects the external genitalia or perineum, and is accompanied by thrombosis of the feeding arteries.[9] The bacteria usually get into the body through cuts or impaired skin barriers, leading to gangrene of the skin and subcutaneous tissue. The infection often progresses rapidly from a local tissue infection to a systemic infection, which may result in severe intoxication, multiple organ failures, septic shock, and ultimately death.[7,9-10]

The time-to-onset of cutaneous vasculitic toxicities in patients with myeloproliferative neoplasm following the initiation of hydroxyurea therapy is widely variable.[5,11] Necrotising fasciitis can progress slowly in several weeks, but it also can affect an entire extremity within 24 hours.[9] Notably, the literature has revealed a high number of delayed diagnoses (median: 6 months), most probably due to the initial paucity of cutaneous findings and the various comorbidities in these patients.[6-7]

In Malaysia, there is one (1) registered product containing hydroxyurea in the oral formulation.[11] To date, the NPRA has received 50 ADR reports with 109 adverse events associated with hydroxyurea use. In addition to the **two (2) local cases of gangrene and Fournier's gangrene** discussed above, the NPRA has also received one (1) report of skin ulcer with purulent discharge suspected to be related to hydroxyurea.[1] At the time of the writing, the World Health Organisation (WHO) global ADR database has recorded 2,165 adverse events (23.2%) involving system organ class (SOC) skin and subcutaneous tissue disorders and 790 adverse events (8.5%) involved SOC Infections and infestations, which were reported with hydroxyurea use. These events (excluding the two cases previously discussed) included skin necrosis (12), necrosis (8), gangrene (7), dry gangrene (1), debridement (2), leg amputation (1), necrotising fasciitis (1), vasculitic ulcer (1), and skin ulcer (304).[12*]

*DISCLAIMER

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## Advice to Healthcare Professionals

1. Be vigilant of the potential risk of cutaneous vasculitis and gangrene associated with hydroxyurea therapy in myeloproliferative disorders, especially in elderly patients with long-term and high-dose hydroxyurea treatment, a history of interferon therapy, and minor trauma at the site of lesions.

2. Consider a lower dosage regimen for those that may be more susceptible to developing cutaneous vasculitis and gangrene, such as elderly or patients with underlying risk factors (e.g., diabetes, smoking, hypertension and hyperlipidaemia, renal failure, peripheral vascular disease, or malignancy).

3. Advise patients taking hydroxyurea to seek medical attention immediately when they develop any skin reactions.

4. If cutaneous vasculitis/gangrene is suspected to be associated with hydroxyurea, discontinue the medication, consider switching to alternative therapy, and institute appropriate treatment (wound care, surgical debridement, and/or pharmacotherapy).

5. Early recognition and prompt management of these cutaneous adverse events are imperative for preventing serious patient outcomes in terms of morbidity, disability, loss of quality of life, and mortality.

6. Report any adverse drug reactions suspected to be related to the use of hydroxyurea to the NPRA.

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## *Articles Based on Case Reports*

# Venetoclax-Induced Tumour Lysis Syndrome

*by Yeoh Hee Sheong*

### *Case Report* [1-2]

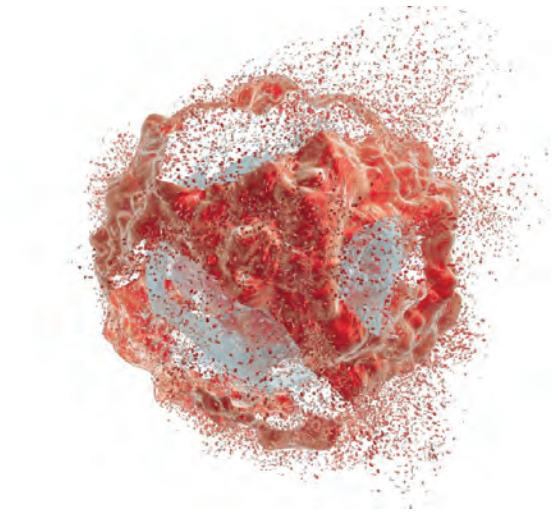
A 59-year old Chinese male was presented to the hospital with complaints of headache, lethargy, and exertional dyspnoea for the past one (1) month. He was pale with a palpable liver and spleen on examination. He had a cadaveric renal transplant 20 years ago for chronic glomerulonephritis-induced end-stage renal disease and had been on long-term oral prednisolone and cyclosporine. Bone marrow and cytometry findings show consistency with T-prolymphocytic leukaemia, indicating a very aggressive course of mature post-transplant lymphoproliferative leukaemia (PTLD) with an unfavourable prognosis.

The patient did not respond to the initial treatment with one cycle of the CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) regime. As the patient was not suitable for alemtuzumab due to the risk of nephrotoxicity in view of his renal allograft, he was later switched to oral venetoclax. On day 15 of treatment, he developed severe **tumour lysis syndrome (TLS)** that needed the support of mechanical ventilation and continuous veno-venous haemodialysis. His white cell count progressively increased to 174 x 109/L, with lymphocytosis predominating. The patient's condition deteriorated and he succumbed to death on day 17, given the poor prognosis of PTLD and TLS complication.

## Discussion

Venetoclax is a B-cell lymphoma-2 (BCL2) inhibitor indicated as a monotherapy or in combination with other medications for the treatment of chronic lymphocytic leukaemia (CLL) and acute myeloid leukaemia (AML). By binding to anti-apoptotic BCL-2 proteins, venetoclax initiates the mitochondrial outer membrane permeabilisation, caspase activation, and eventually programmed cell death.[3]

Tumour lysis syndrome (TLS) is a life-threatening oncological emergency that develops when large amounts of tumour cells are killed or lysed too rapidly, which normally occurs following cytotoxic therapy. The rapid release of electrolytes and intracellular contents causes blood chemistry changes (hyperuricaemia, hyperkalaemia, hyperphosphataemia, and hypocalcaemia), which can potentially lead to renal insufficiency, cardiac arrhythmias, seizures, and in some cases, death.[4-5] Patients with aggressive forms of lymphomas, tumour types with a high proliferative rate, and a large tumour burden are all at risk of developing TLS.[4]



TLS is a commonly reported adverse reaction and a documented important risk for venetoclax.[3] As venetoclax can cause a rapid reduction in tumour, it poses a risk for TLS at initiation and during the ramp-up phase. Changes in blood electrolytes indicative of TLS can occur as early as six (6) to eight (8) hours following the first dose of venetoclax and at each subsequent dose increase, which necessitate prompt management.[3,5] Cases of TLS with severe consequences, including fatal events and renal failure requiring dialysis, have been reported in clinical trials and post-marketing settings in patients treated with venetoclax.[3,5-6] With greater attention to accurate risk stratification and adherence to recommended TLS prophylaxis strategies, the risks of TLS can be minimised, likely translating to better patient outcomes.[6]

Crucially, patients with comorbidities (especially impaired renal function: creatinine clearance <80 mL/min), high tumour burden, and splenomegaly (in CLL) have a higher risk of developing TLS while receiving venetoclax treatment.[3,5] Besides that, venetoclax is predominantly metabolised by CYP3A4, and is both a substrate for and an inhibitor of the P-glycoprotein (P-gp) transporter. Therefore, concomitant use with strong/moderate CYP3A inhibitors (e.g. ketoconazole, posaconazole, and ritonavir) or P-gp inhibitors (e.g. amiodarone, captopril, and felodipine) may increase venetoclax exposure, which in turn raises the risk of TLS.[3]

There are currently three (3) registered products containing venetoclax in Malaysia.[7] To date, NPRA has received a total of 30 adverse drug reaction (ADR) reports with 62 adverse events suspected to be related to venetoclax treatment. The most commonly reported adverse events were neutropenia (7), followed by pyrexia (4) and febrile neutropenia (3).[1] At the time of writing, there was **one (1) local report of tumour lysis syndrome**, as discussed above, while the World Health Organisation (WHO) international ADR database has recorded 553 global reports of TLS suspected to be linked to venetoclax use.[1,8*]

*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

1 Be aware that venetoclax can cause tumour cells to lyse too rapidly, and thus poses a risk for TLS at treatment initiation and during the dose-titration phase.

2 Before starting venetoclax, it is crucial to perform risk assessment for TLS in all patients, which include baseline renal function, blood chemistries, comorbidities, tumour burden, and the presence of splenomegaly (in CLL).

3 Promptly correct blood chemistry abnormalities prior to drug initiation and during treatment, as these conditions can be fatal if left untreated.

4 When treating patients with venetoclax, always adhere to clinical guidance on appropriate prophylactic measures (including hydration and anti-hyperuricaemics), laboratory monitoring (including blood chemistries), dose titration, and drug interactions.

5 Educate patients about the symptoms of TLS and measures to reduce the risk of TLS (for example, drinking plenty of water).

6 Advise patient to stop taking venetoclax and seek medical attention immediately when they develop any of the signs and symptoms of TLS, including fever, chills, confusion, unusual tiredness, shortness of breath, and dark or cloudy urine.

7 Report any adverse events suspected to be associated with venetoclax use to the NPRA.

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*Articles Based on Case Reports*

# Atypical Antipsychotics: Risk of Urinary Retention

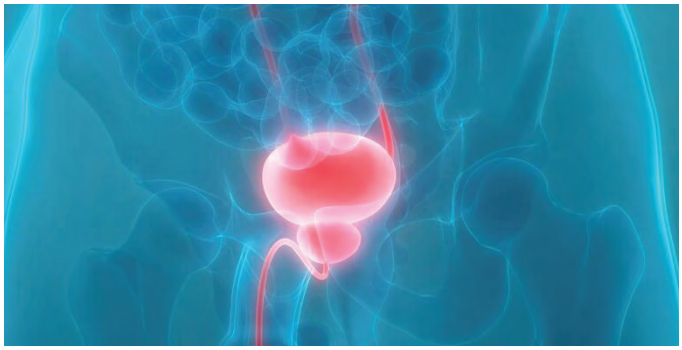
*by Nurul Aimi binti Mohd Reduzan*

### *Case Report 1*[1]

A 35-year-old Chinese male received an intramuscular injection of fluphenazine 12.5 mg STAT for acute psychosis and later started on oral olanzapine 5 mg in the morning and 10 mg at night for the treatment of schizophrenia. Four (4) days later, the patient developed **acute urinary retention**, and olanzapine was switched to oral aripiprazole 5mg daily. On the 11th day after switching of drug, the patient had not yet recovered at the time of reporting, and a closed bladder drainage had been inserted.

### *Case Report 2*[1]

A 40-year-old indigenous male was initiated on oral olanzapine for schizophrenia treatment with a morning dose of 10 mg and a night dose of 25 mg. One (1) day after receiving the drug, the patient claimed of **dysuria** along with **pain in the suprapubic region**. The patient informed that the condition had persisted for four (4) days, and he was hospitalised. Following the withdrawal of olanzapine, the patient made a full recovery.



## Discussion

Atypical antipsychotics, or second-generation antipsychotics, are commonly used in the treatment of psychiatric conditions such as schizophrenia and bipolar affective disorder.[2] Asenapine, clozapine, olanzapine, quetiapine, paliperidone, risperidone, ziprasidone, amisulpride, and aripiprazole are among the atypical antipsychotics available in Malaysia.[3]

Urinary retention is an inability to completely empty the bladder despite persistent effort. This condition can be acute or chronic, with acute cases generally accompanied by suprapubic pain, bloating, urgency, or distress.[4-5] There are multiple aetiologies for urinary retention, including obstructive [e.g. benign prostatic hyperplasia (BPH)], infectious and inflammatory, neurogenic (e.g. diabetes mellitus associated with nerve lesions), and pharmacologically induced.[5-7] Urinary retention has been commonly described with the use of drugs with anticholinergic activity (e.g. anticholinergic respiratory agents, antipsychotics, and antidepressants), opioids and anaesthetics, α-adrenoceptor agonists, benzodiazepines, NSAIDs, and calcium channel antagonists.[5-6]

Atypical antipsychotics are known to demonstrate a broad and diverse pharmacologic profile across a number of receptor systems (e.g. serotonin, dopamine, cholinergic muscarinic, alpha-adrenergic and histamine).[2] Among the atypical antipsychotics, anticholinergic effects have been described for urinary retention associated with clozapine and olanzapine.[6-7] For certain atypical antipsychotics, such as risperidone and ziprasidone, acute urinary retention has been linked to the result of serotoninergic mechanism in combination with dopaminergic inhibition and adrenergic stimulation.[6] Amisulpride, which does not display significant affinity for cholinergic muscarinic and alpha-adrenergic receptors, might inhibit voiding ability via inhibition of dopamine receptor.[8]

While most clinicians keep a careful eye on extrapyramidal side effects, it has been highlighted that urinary retention is often overlooked following the use of atypical antipsychotics.[7] Acute urinary retention, if left untreated, can lead to infection, acute kidney injury, and renal failure. A Canadian population-based cohort study has reported that quetiapine, risperidone and olanzapine were associated with a higher 90-day risk for hospitalisation with acute kidney injury and other

adverse outcomes in patients aged 65 years or older, including acute urinary retention [relative risk: 1.98 (CI: 1.63-2.40)].[9] Elderly are often associated with comorbidities or underlying conditions, such as constipation, diabetes mellitus, impaired physical mobility, and concomitant use of medication, that could further reinforce the impairing effect on micturition. Elderly male patients are at an increased risk of developing drug-induced urinary retention, owing to the high prevalence of BPH in this group.[6]

As of May 2022, NPRA has received **eight (8) reports of urinary retention** suspected to be related to atypical antipsychotics, involving olanzapine (2 reports, including *case report 1*), quetiapine (3), clozapine (2) and risperidone (1). In addition, there were three (3) local reports of dysuria associated with atypical antipsychotics, one each for olanzapine [*case report 2*], quetiapine and risperidone.[1] A search on the World Health Organisation (WHO) database at the time of writing revealed a total of 2,047 global reports of urinary retention involving quetiapine (567), risperidone (442), olanzapine (421), aripiprazole (311), clozapine (293), ziprasidone (78), paliperidone (70), amisulpride (46), and asenapine (15).[10*]

NPRA has reviewed this safety issue and a directive [Ref. No.: (26) dlm. BPFK/PPP/07/25 Jld.2] has been issued requiring all local package inserts and consumer medication leaflets of products containing atypical antipsychotic (asenapine, clozapine, olanzapine, quetiapine, paliperidone, risperidone, ziprasidone, amisulpride, and aripiprazole) to be updated with the risk of urinary retention.

*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

1 Be aware of the risk of urinary retention associated with atypical antipsychotic use.

2 Prescribe atypical antipsychotics with caution in patients with a history of urinary retention or risk factors for urinary retention (e.g. elderly, men, underlying BPH, neurological comorbidities, or taking concomitant medications with anticholinergic activity).

3 Proactively monitor patients' renal function shortly following drug initiation or dose increase.

4 Advise patients to seek immediate medical attention if they experience any signs and symptoms of urinary retention.

5 When drug-induced acute urinary retention is suspected, initiate urinary catheterisation and concurrent pharmacotherapy, in combination with discontinuation or dose reduction of the causative drug.

6 Report all suspected adverse reactions related to atypical antipsychotic use to the NPRA.

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## What's New?

# List of Directives Related to Drug Safety Issues

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 and consumer medication leaflets (RiMUP) of all products containing the affected active ingredients are updated with the required safety information. The table below shows the DCA directives that were recently issued, which are available on the NPRA website.

| | Active Ingredient | Safety Issue | Date | Directive Ref. No. |
|---|---|---|---|---|
| 1 | Sulfamethoxazole & Trimethoprim (Co-Trimoxazole) | Risk of Acute Respiratory Distress Syndrome (ARDS) | 11-Apr-2022 | [NPRA.600-1/9/13 (3) Jld.1] |
| 2 | Warfarin | Risk of Anticoagulant-Related Nephropathy (ARN) | 11-Apr-2022 | [NPRA.600-1/9/13 (4) Jld.1] |
| 3 | Hydrochlorothiazide, Chlorthalidone, Indapamide and Acetazolamide | Risk of Choroidal Effusion, Acute Myopia & Acute Angle-Closure Glaucoma | 11-Apr-2022 | [NPRA.600-1/9/13 (5) Jld.1] |
| 4 | Corticosteroids (Systemic) | Risk of Pheochromocytoma Crisis | 13-Jul-2022 | [NPRA.600-1/9/13 (6) Jld.1] |
| 5 | Azathioprine | Risk of Erythema Nodosum and Hypersensitivity Reactions | 13-Jul-2022 | [NPRA.600-1/9/13 (7) Jld.1] |
| 6 | Chloroquine and Hydroxychloroquine | Risk of Psychiatric Disorders | 13-Jul-2022 | [NPRA.600-1/9/13 (8) Jld.1] |

## How to report adverse events?

NPRA encourages all healthcare professionals to report all suspected adverse drug reactions (ADRs) to medicines (including over-the-counter medicines, traditional products, and health supplements) as well as adverse events following immunisation (AEFIs) with vaccines.

To report adverse events:

1. Visit **www.npra.gov.my**
2. Report ADRs/AEFIs **as healthcare professional**
   a) Choose **online reporting**; or
   b) Download the **manual reporting 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, complete the **subscription form** available on NPRA website, or send an email with your details to **fv@npra.gov.my**





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