



TO REPORT AN ADVERSE DRUG REACTION

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1. Visit www.bpfk.gov.my.
2. Click on ADR Reporting and Product Complaints.
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The Drug Safety Monitoring Centre, Centre for Post Registration of Products, National Pharmaceutical Control Bureau, Ministry of Health, PO Box 319, Jalan Sultan, 46730 Petaling Jaya, Selangor.

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Reaksi

DRUG SAFETY NEWS

Mission: This publication provides information and recommendations to healthcare professionals to enhance communication of drug safety updates, raise awareness of adverse drug reactions reported, and stimulate additional adverse drug reaction reporting.

This is a bimonthly publication by the Drug Safety Monitoring Centre, National Pharmaceutical Control Bureau (NPCB), Malaysia.

In This Issue:

Zofran[®] (ondansetron), Kytril[®] (granisetron) and Aloxi[®] (palonosetron):

5-HT₃ Receptor Antagonist-associated Serotonin Syndrome



Zofran® (ondansetron), Kytril® (granisetron) and Aloxi® (palonosetron): 5-HT₃ Receptor Antagonist-associated Serotonin Syndrome

Overview of Serotonin Syndrome

Serotonin syndrome is an adverse drug reaction (ADR) that causes high levels of the neurotransmitter 5-hydroxytryptamine - 5HT (serotonin), to accumulate in the body. Classical features include mental status changes, autonomic instability, and neuromuscular hyperactivity (please refer to **Table 1** for list of symptoms associated with serotonin syndrome)¹. The term "serotonin syndrome" is often used to refer to the severe end of the toxicity spectrum.

Diagnosis of serotonin syndrome is based on clinical judgement and can be challenging. Mild symptoms can be mistaken for an exacerbation of psychiatric symptoms, and more severe cases for conditions such as neuroleptic malignant syndrome (NMS) or malignant hyperthermia. Other differential diagnoses to consider include anticholinergic toxicity, serotonergic discontinuation syndrome, sympathomimetic drug intoxication, meningitis, encephalitis, heat stroke, and central hyperthermia.

Any drug that directly or indirectly increases central serotonin neurotransmission can induce serotonin syndrome (please refer to **Table 2** for medications associated with serotonin syndrome)². Studies have shown that involvement of postsynaptic 5HT-1A and 5HT-2A receptors are particularly important³.

Table 2: Medications Which May Contribute to Serotonin Syndrome

Amphetamines and derivatives

- Ecstasy, dextroamphetamine, methamphetamine, sibutramine

Analgesics

- Fentanyl, tramadol

Antidepressants/mood stabilizers

- Buspirone
- Lithium
- Monoamine oxidase inhibitors
- Selective serotonin reuptake inhibitors
- Serotonin-norepinephrine reuptake inhibitors
- Serotonin 2A receptor blockers
- St. John's wort (*Hypericum perforatum*)
- Tricyclic antidepressants

Antiemetics

- Metoclopramide
- 5-HT₃ receptor antagonists

Antimigraine/ anticonvulsant drugs

- Carbamazepine, ergot alkaloids, triptans, valproic acid

Miscellaneous

- Cocaine, dextromethorphan, linezolid, L-tryptophan, 5-hydroxytryptophan

Table 1: Symptoms Associated With Serotonin Syndrome

Symptom Cluster	Symptomatology
Altered mental status	Agitation, anxiety, disorientation, restlessness, excitement
Neuromuscular abnormalities	Tremors, clonus, hyperreflexia, muscle rigidity, bilateral Babinski signs, akathisia
Autonomic hyperactivity	Hypertension, tachycardia, tachypnoea, hyperthermia, mydriasis, diaphoresis, dry mucous membranes, flushed skin, shivering, vomiting, diarrhoea, arrhythmias

Background of the Safety Issue

The 5-HT₃ receptor antagonists granisetron, ondansetron and palonosetron have been linked with a potential risk of serotonin syndrome when used concomitantly with other serotonergic medicines. These medicines are used to prevent nausea and vomiting after surgery and in patients undergoing cancer treatment. They work by blocking serotonin from entering certain cells in the nervous system and brain.

In 2012, an article in the World Health Organization (WHO) Pharmaceuticals Newsletter highlighted that ondansetron used together with other drugs that affect serotonin levels (serotonergic drugs) may contribute to the development of serotonin syndrome in susceptible patients^{4,5}.

Following this, the NPCB conducted a review of this safety issue, which showed that when used as indicated, serotonin-blocking drugs used alone to treat nausea and vomiting are unlikely to cause serotonin syndrome. However, when these drugs are used in combination with other products that affect serotonin levels, the way they work together in the body could lead to development of serotonin syndrome.

Local Scenario

There are ten (10) products containing ondansetron, six (6) containing granisetron and one (1) product containing palonosetron registered with the Drug Control Authority.

The product registration holders for the innovator products: Zofran® (ondansetron), Kytril® (granisetron), and Aloxi® (palonosetron) have submitted safety updates to incorporate the risk of serotonin syndrome into the 'Warnings and Precautions' section of the package inserts.

Adverse Drug Reaction Reports

Since the year 2000, the NPCB Drug Safety Monitoring Centre has received 13 ADR reports for **ondansetron** (adverse events include burning sensation, headache,

injection site rash, jerky movement, nose congestion, teary eyes), seven (7) reports related to **granisetron** (including agitation, anxiety, body ache, breath shortness, giddiness, increased sweating, rash, vomiting), and one (1) report for **palonosetron** reporting the adverse event palpitations.

Advice for Healthcare Professionals:

- Healthcare professionals and patients need to be aware of the potential for toxicity from serotonergic drugs. Early recognition and treatment of serotonin syndrome can prevent significant morbidity and mortality.
- Avoid the combined use of serotonin-augmenting drugs as far as possible. Caution must be taken if two serotonergic drugs are used together.
- Management:
 - i) withdraw the serotonergic drugs
 - ii) provide supportive care (e.g. stabilise vital signs, keep oxygen saturation above 93%, continuous cardiac monitoring, sedation with benzodiazepines, hospital admission).
- If the diagnosis is unclear, all serotonergic agents should be stopped and supportive care given.
- All ADRs suspected to be related to 5-HT₃ receptor antagonist use should be reported to the NPCB.

References:

1. Volpi-Abadie J, Kaye AM et al. (2013). *Serotonin Syndrome*. The Ochsner Journal 13: 533–540.
2. Ables AZ and Nagubilli R (2010). *Prevention, Diagnosis, and Management of Serotonin Syndrome*. Am Fam Physician. 81 (9):1139-1142.
3. Boyes EW and Shannon M (2005). *The serotonin syndrome*. N Engl J Med 352:1112-20.
4. Health Canada (2014). *New safety information: Risk of serotonin syndrome associated with serotonin blocking drugs used to treat nausea and vomiting*. [healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2014/39519a-eng.php].
5. TGA (2014). *Safety advisory - risk of serotonin syndrome*. [www.tga.gov.au/alert/serotonin-blocking-medicines-used-treat-nausea-and-vomiting].