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Kigali on; 11/08/2021
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DIRECT HEALTHCARE PROFESSIONAL COMMUNICATION

Re: Signal of hyponatremia following use of Tramadol

Dear Healthcare professionals,

Tramadol is an opioid analgesic for treatment of moderate to severe pain. It is a non-selective pure agonist at μ-, δ- and κ-opioid receptors with a higher affinity for the μ-receptor. Other mechanisms for its analgesic effect involve inhibition of serotonin- and noradrenaline reuptake. To exert full analgesic effect tramadol must be converted by CYP2D6 to its main metabolite O-desmethyltramadol (M1) which has a several-fold higher affinity for μ-opioid receptors than the parent drug. Tramadol is also converted by CYP3A4 and CYP2B6 to an inactive metabolite [1].

The inhibition of CYP3A4 and CYP2D6 may affect the plasma concentration of tramadol. Tramadol and its metabolites are almost completely excreted via the kidneys. An elimination half-life of up to three times longer than normal has been observed in patients with renal insufficiency. A signal of hyponatremia associated with Tramadol was investigated and analysed by WHO-UMC based on vigibase data [1, 2].

Hyponatraemia (HN) is characterised by serum sodium <135 mmol/L and is considered severe at <125 mmol/L. It is especially common among elderly and hospitalised patients with comorbidities and who are taking many drugs. Symptoms may include nausea, headache, decreased level of consciousness, seizures, impaired mental status [3].
There are several possible mechanisms of actions for tramadol-induced Hyponatremia, involving the opioid, serotonin and noradrenaline pathways. However, these neurotransmitters are all active in very complex mechanisms. Therefore, the exact mechanisms for tramadol-induced Hyponatremia may be difficult to fully understand.

VigiBase cases that support causality between tramadol and hyponatraemia were found. The key cases usually concerned elderly and predisposed patients, but young individuals were also identified. Causality was supported by the time-to-onset pattern, cases with positive dechallenge and one positive rechallenge. It found that the use of tramadol was associated with an increased risk of hyponatremia requiring hospitalization [4].

Patients and healthcare professionals should be aware of the risk of tramadol-induced Hyponatremia, particularly in cases concerning elderly and predisposed patients, and when there is co-treatment with other drugs known to cause Hyponatremia.
Rwanda FDA has reviewed information on the signal of hyponatremia and tramadol and formulated the following recommendations:

Information for healthcare professionals

- Health-care professionals should be aware of this potential adverse reaction and weight the benefits of prescribing tramadol to patients because of increased risk of hyponatremia.
- Rwanda FDA advice Health care professionals to consider monitoring serum sodium levels and any signs or symptoms of hyponatremia when administered tramadol parentally.
- Healthcare professionals should not prescribe tramadol when a patient is receiving concomitant medications known to cause hyponatremia.
- Educate patients how to recognize the signs and symptoms of hyponatremia.

Rwanda FDA urges patients and healthcare providers to report the suspected adverse drug reactions related to tramadol and other medicines to Rwanda FDA by filling information in online reporting system accessible on https://pvims.rwandafda.gov.rw/public/spontaneous or by completing ADR/AEFI reporting form accessible on Rwanda FDA website on the link http://w.w.w.rwandafda.gov.rw/web/fileadmin/adr-aefi_reporting_form.pdf and the filled form should be sent to the email: pv_sm@rwandafda.gov.rw and copy to info@rwandafda.gov.rw.

Sincerely,

RWANDA FOOD AND DRUGS AUTHORITY - RWANDA FDA

Dr. Charles KARANGWA
Ag. Director General

References

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4. Spigset O, Hedenmalm K. Hyponatremia in relation to treatment with antidepressants: a survey of reports in the World Health Organization database for spontaneous reporting of adverse drug reactions. Pharmacotherapy 1997; 17:348-52.