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SAFETY INFORMATION COMMUNICATION

Medicine	Title
Gapentin	**Risk of drug dependence among patients using Gabapentin**

1. Introduction

Reference is made to the safety reports analysis conducted by Rwanda FDA on the potential risk of drug dependence among patients using Gabapentin;

It is in this regard that Rwanda FDA analyzed the potential risk of drug dependence associated with the use of Gabapentin for appropriate regulatory action including communicating this important risk to healthcare professionals and patients for adoption of adequate risk minimization measures.

2. Description of the safety information

Gabapentin is therapeutically classified as a Gabapentinoid used in the treatment of chronic pain and seizures. [1] Gabapentin has been shown to lead to dependence, addiction and withdrawal in some people, although when it was first approved in 1993 this risk was thought to be minimal.

Gabapentin has been increasingly associated with drug abuse, particularly in people who mix it with opioids, alcohol or other substances. [2] The dose-related GABA mimetic action causing euphoria is the contributing factor in its potential abuse and individual variability in GABA-mimetic euphoric action can be the reason that abuse is not seen in majority of the patients. [3]
Gabapentin has a cyclohexyl group to the structure of neurotransmitter GABA as a chemical structure. Even though it has a similar structure to GABA, it does not bind to GABA receptors and does not influence the synthesis or uptake of GABA. [4] Gabapentin works by showing a high affinity for binding sites throughout the brain correspondent to the presence of the voltage-gated calcium channels, especially alpha-2-delta-1, which seems to inhibit the release of excitatory neurotransmitters in the presynaptic area that participate in epileptogenesis. [4]

Even though there is no evidence for direct action at the serotonin, dopamine, benzodiazepine, or histamine receptors, research has shown gabapentin to increase total-blood levels of serotonin in healthy control subjects. [4] Although the exact molecular mechanisms by which these agents act to produce their intoxicating effects are not completely understood, many drugs of abuse are known to bind to specific neuronal membrane proteins that produce effects on cellular signaling and ultimately on behavior. With repeated administration of a drug, individuals often develop tolerance, and discontinuation of drug use following chronic administration typically results in withdrawal symptoms. [5]

Although no cases of drug dependence among patients using Gabapentin have been reported in Rwanda, around

664 cases recorded in WHO global database (VigiLyze) as of 22nd October, 2023. These case reports were retrieved from the WHO global database, VigiLyze, using "Gabapentin (Active ingredient)" as the search criteria for the drug and "drug dependence (PT)" as the search criteria for the reaction. The analysis of global case reports shows a consistency, temporal relationship of the drug-event combination.

Other drugs belonging in the same therapeutic category as Gabapentin were used and drug dependence is labelled in their SmPC. These drugs are Pregabalin and Clonazepam. [6]

It was observed that drug dependence is labelled in Gapentin Summary of Product Characteristcis (SmPC) of UK available at electronic medicines compendium in the section 4.8 of undesirable effects with unknown frequency. [7] However, the submitted SmPCwas not labelled in the SmPCs of Gabapentin, specifically SmPC of NEUROBA and GABAPENTIN capsules 300 mg submitted to Rwanda FDA, [8,9] Yet, Additionally, EMA CMDh scientific conclusions for Gabapentin and grounds for the variation to the amendment of product information, highlighted withdrawal symptoms that might be indicative of drug dependence and are of clinical significance with opinion to add information to SmPC sections 4.4 and 4.8, in line with the pregabalin product information, including the additional withdrawal symptoms that were described in literature and spontaneous case reports. [10]

Rwanda FDA warns healthcare professionals about the potential risk of drug dependence among patients using Gabapentin, Gabapentin should be used with precautions especially in patients under other drugs that can lead to the similar event of drug dependence.

3. *Information to Consumers/Patients/Caregivers*

- Patients should be aware of a potential risk of drug dependence when using Gabapentin.
- Patients are encouraged to report any suspected or encountered adverse event associated with the use of Gabapentin to healthcare professionals and/or to Rwanda FDA using existing reporting channels.

4. *Information to Healthcare Professionals*

- Healthcare professionals should be aware of the potential risk of drug dependence associated with the use of Gabapentin
- Healthcare professionals are requested to monitor patients under Gabapentin therapy especially those on concomitant medications that can induce drug dependence.
- Healthcare professionals are requested to collect and submit any case report to Rwanda FDA of any suspected or encountered adverse event in order to guide the Authority on further assessment of serious adverse events and take appropriate regulatory actions.

5. *Information to Manufacturers/Marketing Authorization Holders*

- Marketing Authorization Holders are requested to revise the SmPC submitted to Rwanda FDA and include the risk of drug dependence in section of undesirable adverse reactions and in the section of warnings and precautions

- Marketing Authorization Holders are recommended to continuously provide update of global experience of Gabapentin use through submission of aggregated reports (PSUR/PBRER) and risk management plans to Rwanda FDA.

6. *Reporting Channel*

Patients and Healthcare Professionals are urged to report any suspected serious adverse drug reaction associated with Gabapentin and other medicines/vaccines to Rwanda FDA by completing ADR/AEFI reporting form

accessible on Rwanda FDA website via the link **https://rwandafda.gov.rw/wp-content/uploads/2022/11/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,

Prof. Emile BIENVENU
Director General

7. *References*

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