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South African
Health Products
Regulatory Authority

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MEDICINE SAFETY ALERT

Warfarin and Tramadol – Harmful Drug-Drug Interaction

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The South African Health Products Regulatory Authority (SAHPRA) would like to inform healthcare professionals about the risk of a drug-drug interaction (DDI) associated with concomitant use of warfarin and tramadol. Taking these two medicines simultaneously can lead to an increase in the International Normalised Ratio (INR), and result in severe ecchymosis and bleeding, which may lead to death. Although the mechanism has not been elucidated, occasional reports of elevated INR, ecchymosis and/or bleeding have been identified in patients taking warfarin after starting tramadol, however, cases of major bleeding have been reported to be rare, while fatal cases are even rarer. The interaction usually occurs 3-4 days after tramadol is commenced in patients stabilised on warfarin. The decrease in INR after tramadol is withdrawn may take several days. As warfarin has a narrow therapeutic index, extra caution is required when co-prescribing medicines, due to the possibility of interactions that could lead to an increased or diminished anticoagulant response.

Warfarin is a member of the coumarin-type anticoagulants. It acts in the liver by inhibiting the synthesis of Vitamin K dependent coagulation factors. The resultant in vivo effects include the sequential depression of Factors Vll, IX, X and II and the anticoagulant factors protein C and S. Warfarin is indicated for the prevention and management of deep vein thrombosis and pulmonary embolism, and the prevention of thromboembolism in atrial fibrillation, prosthetic heart valves, post myocardial infarction, and the treatment of transient ischaemic attacks.

Tramadol is a non-selective opioid analgesic, which acts as an agonist at the mu, delta, and kappa opioid receptors. It is indicated for the management of moderate to moderately severe pain in adults and not recommended for minor pain that may be treated adequately through lesser means. The PI for tramadol states that healthcare professionals should exercise caution during concomitant treatment with coumarin derivatives such as warfarin, due to reports of increased INR resulting in severe bleeding and/or ecchymosis and may lead to death.

To minimise the risk of drug interactions between the two medicines, healthcare professionals are advised to take the following measures (non-exhaustive):

- Consider if additional INR monitoring is required when starting tramadol or another concomitant medicine.
- Determine if a dose adjustment or therapeutic monitoring is required.
- Ensure that patients are aware of the need to seek medical treatment and have an urgent INR test should they experience any of the following symptoms:
    - Bleeding for more than 10 minutes.
    - Blood in vomit, sputum, stool, or urine.
    - Severe or unexplained bruising.
    - Severe bleeding gums.
    - Unusual headaches with blurred vision, slurred speech, loss of movement, feeling or being sick, convulsions, loss of consciousness and/or dizziness.
    - Women who experience heavy or increased bleeding during their menstrual period or any other heavy vaginal bleeding.

Patients should be advised:

- To inform their healthcare professionals that they are on warfarin treatment.
- Not to stop taking warfarin and not to take any new medicines without discussing with their healthcare professionals.

Healthcare professionals are:

- Requested to urgently draw the attention of all involved personnel in their area of responsibility to the risk of a DDI associated with concomitant use of warfarin and tramadol.
- Urged to report any adverse drug reactions (ADRs), or product quality problems to SAHPRA via the following eReporting link: https://vigiflow-eforms.who-umc.org/za/ereporting or complete the ADR reporting form accessible via https://www.sahpra.org.za/wp-content/uploads/2023/11/GLF-CEM-PV-06A_v3-Adverse-Drug-Reactions-and-Quality-Problem-Reporting-Form.pdf and email it to adr@sahpa.org.za. Alternatively, reporting can be done via the Med Safety App, downloadable through Google Play or App Store. For more information regarding the app, please visit https://medsafety.sahpra.org.za/.

Please provide as much information as possible, including information about batch numbers, medical history, any concomitant medication, onset timing, treatment dates, and product brand name. Your report will help SAHPRA to safeguard public health.

References:

1. Medicines and Healthcare Products Regulatory Agency (MHRA) – Safety Communication (Published 20 June 2024). https://www.gov.uk/drug-safety-update/warfarin-be-alert-to-the-risk-of-drug-interactions-with-tramadol#:~:text=Taking%20warfarin%20and%20tramadol%20together,some%20patients%20could%20be%20fatal (Accessed 16 May 2025).
2. Ruth Savage, Medical Assessor, CARM, New Zealand Pharmacovigilance Centre, Dunedin. Evidence of interaction between warfarin and tramadol. Prescriber Update 27(2):23-24. October 2006 https://www.medsafe.govt.nz/profs/puarticles/tramwarf.htm (Accessed 16 May 2025).
3. PI for Tramadol capsule (Approved 21 February 2025). https://pi-pil-repository.sahpra.org.za/wp-content/uploads/2025/03/Tramadol-Unimed_Approved-PI_v2_20250221.pdf (Accessed 16 May 2025).
4. PI for warfarin (Approved 30 September 2023) https://pi-pil-repository.sahpra.org.za/wp-content/uploads/2023/10/1.3.1.1-approved-pi-warfarin-5-biotech-sept-2023.pdf (Accessed 16 May 2025).

About SAHPRA

SAHPRA is tasked with regulating (monitoring, evaluating, investigating, inspecting and registering) all health products. This includes clinical trials, complementary medicines, medical devices and in-vitro diagnostics (IVDs). Furthermore, SAHPRA has the added responsibility of overseeing radiation control in South Africa. SAHPRA's mandate is outlined in the Medicines and Related Substances Act (Act No 101 of 1965, as amended) as well as the Hazardous Substances Act (Act No 15 of 1973).

SAHPRA has three pillars to ensure that medicines, medical devices and IVDs meet the requisite standards to protect the health and well-being of all who reside in South Africa:

- Safety
- Efficacy
- Quality

It is these three pillars that define the ethos of SAHPRA.