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Varenicline:
Risk of loss of consciousness

Quick Read

Varenicline (Champix®) can cause dizziness and somnolence, and can also be associated with episodes of loss of consciousness. Patients are advised not to drive, operate complex machinery or undertake potentially hazardous activities until it has been confirmed that the medicine does not affect their ability to perform those activities.

Varenicline is indicated for helping adults to quit smoking. It binds neuronal α4β2 nicotinic acetylcholine receptors with high affinity and selectivity. Acting as a partial agonist it causes dopamine to be released, which produces the same effects as nicotine though with much lower intensity and without withdrawal effects. On the other hand, it prevents exogenous nicotine to bind to nicotinic cholinergic receptors, thus blocking the effects from the sustained use of nicotine (antagonist effect). Varenicline is metabolized to a very small extent and is 92% excreted unaltered in urine.

A total of 1,129 cases have been reported of loss of consciousness with varenicline, according to the European adverse drug reaction database Eudravigilance. In seventeen post-marketing cases causality was confirmed. In Portugal only one suspected case has been reported for which clinical assessment did not demonstrate a causal relationship.

The PRAC at EMA has meanwhile concluded that there is evidence for an association between varenicline and loss of consciousness; varenicline can stimulate the **release of gamma-aminobutyric acid (GABA)**, a major central nervous system inhibitor neurotransmitter.

Given the data available from Eudravigilance and from the literature, the PRAC recommends that the information for varenicline-containing products be updated to include the undesirable effect "**Transient loss of consciousness**" in section 4.8 of the SPC (the PL will be updated accordingly).

Additionally, section 4.7 (**Effects on ability to drive and use machines**) will stress that, since varenicline may cause dizziness, somnolence and transient loss of consciousness, patients are advised not to drive, operate complex machinery or engage in other potentially hazardous activities until it is known whether the medicinal product affects their ability to perform those activities.

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Interaction between apixaban or edoxaban and selective serotonin reuptake inhibitors and/or serotonin-noradrenaline reuptake inhibitors: increased risk of haemorrhage

Quick Read

Similarly to platelet aggregation inhibitors and NSAIDs, there is increased bleeding risk when direct anticoagulants (apixaban, edoxaban) are given concomitantly with SSRIs/SNRIs.

Apixaban and edoxaban are direct anticoagulants which inhibit factor Xa.

Apixaban is indicated for:

- *Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery*
- *Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA); age ≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥ II).*
- *Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.*

Edoxaban is indicated for:

- *Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA).*
- *Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.*

In December 2017, the UK medicines agency detected in its database several cases of bleeding associated with concomitant use of apixaban or edoxaban and antidepressants from the selective serotonin reuptake inhibitor and/or serotonin-noradrenaline reuptake inhibitor classes.

Taking into account the cases in the European adverse drug reaction report database Eudravigilance and in the literature[1-3], as well as the supplementary information provided by the Marketing Authorization Holders and this interaction's biological plausibility, the PRAC agreed in May 2018 that changes should be introduced in the SPC texts, which will read as follows:

Apixaban

4.4. Special warnings and precautions for use

Interaction with other medicinal products affecting haemostasis

[…]

Care is to be taken if patients are treated concomitantly with selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs), or non-steroidal anti-inflammatory drugs (NSAIDs), including acetylsalicylic acid.

4.5. Interaction with other medicinal products and other forms of interaction

Anticoagulants, platelet aggregation inhibitors, SSRIs/SNRIs and NSAIDs

[…] there may be individuals with a more pronounced pharmacodynamic response when antiplatelet agents are coadministered with apixaban. Eliquis should be used with caution when coadministered with SSRIs/SNRIs or NSAIDs (including acetylsalicylic acid) because these medicinal products typically increase the bleeding risk. A significant increase in bleeding risk was reported with the triple combination of apixaban, ASA and clopidogrel in a clinical study in patients with acute coronary syndrome (see section 4.4).

Edoxaban

4.4. Special warnings and precautions for use

Interaction with other medicinal products affecting haemostasis

Concomitant use of medicines affecting haemostasis may increase the risk of bleeding. These include acetylsalicylic acid (ASA), P2Y12 platelet inhibitors, other antithrombotic agents, fibrinolytic therapy, selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs), and chronic nonsteroidal anti-inflammatory drugs (NSAIDs) (see section 4.5).

4.5. Interaction with other medicinal products and other forms of interaction

Anticoagulants, antiplatelets, NSAIDs and SSRIs/SNRIs

[…]

SSRIs/SNRIs: As with other anticoagulants the possibility may exist that patients are at increased risk of bleeding in case of concomitant use with SSRIs or SNRIs due to their reported effect on platelets (see section 4.4).

Márcia Silva

References:

[1] *Allen SN et al. Treatment of Depression in Patients on Anticoagulation Therapy: Antidepressant – Warfarin Drug Interactions. US Pharm 2013; 38(11): 23-26.*

[2] *Spina E et al. Clinically Significant Drug Interactions with Newer Antidepressants. CNS Drugs 2012; 26(1): 39-67.*

[3] *Sigawy et al. Spontaneous hemopericardium in a patient receiving apixaban therapy: first case report. The Journal of Human Pharmacology and Drug Therapy. 2015;5:e115-e117.*

Communications to Healthcare Professionals published on the Infarmed website

Click on the links.

INN Medicinal product	Target	Comunication Online publication date
Hydroxyethyl starch (HES) Tetraspan Venofundin Volulyte Voluven Fresenius	**Physicians:** specialists in anaesthesiology, infectious diseases, nephrology and surgery; physicians at intensive care and burn units; emergency service directors. **Nurses:** head nurses at emergency services, as well as at intensive care and burn units and operating theatres. **Pharmacists:** directors of hospital pharmaceutical services.	New measures to reinforce existing restriction due to increased risk of renal impairment and mortality in patients in critical condition or with sepsis. 07-08-2018
Olaparib Lynparza – until film-coated tablets begin to be marketed (context of conditional authorization)	**Pharmacists:** directors of pharmaceutical services in hospitals applying for special conditional authorization. **Physicians:** prescribers in the above context.	Risk of medication errors with new pharmaceutical form (tablets vs. capsules). 27-08-2018
Radium (223Ra) dichloride Xofigo	**Physicians:** oncologists and urologists (specialized in prostate cancer); specialists in nuclear medicine. **Pharmacists:** pharmaceutical services in hospitals with nuclear medicine units.	New indication restrictions due to increased risk of fractures and increased mortality trend. 06-08-2018

Compiled by Fernanda Marques

Educational Materials published in the Infomed product information webpage

Click on the links.

INN Medicinal product	Target	Materials? Online publication date
Crizotinib Xalkori	**Patients**	Guide – safety information 01-08-2018
Efavirenz + Emtricitabine + Tenofovir Emtricitabine + Tenofovir Tenofovir Efavirenz + Emtricitabina + Tenofovir Teva Emtricitabina + Tenofovir Teva Tenofovir Teva	**Physicians:** infectious diseases, internal medicine, gastroenterology, and paediatrics.	Safety information on renal function monitoring and posology adjustments for Tenofovir Teva and Emtricitabina + Tenofovir Teva in adolescent patients with chronic hepatitis B and/or with HIV infection.
	Physicians: infectious diseases, internal medicine, and gastroenterology.	Safety information on renal function monitoring and posology adjustments for Tenofovir Teva and Emtricitabina + Tenofovir Teva in adult patients. 01-08-2018

Educational Materials published in the Infomed product information webpage

Click on the links.

INN Medicinal product	Target	Materials? Online publication date
Emtricitabine + Tenofovir Emtricitabina + Tenofovir Sandoz	**Physicians:** infectious diseases and internal medicine.	Recommendations on renal monitoring in paediatric patients with HIV-1 infection. 01-08-2018
Fentanyl Breakyl – 200 µg, 400 µg e 600 µg	**Physicians:** in pain treatment and palliative care units, and in oncology services.	Educational brochure on risk minimization.
	Patients	Educational brochure on risk minimization. 22-08-2018
Tocilizumab Roactemra	**Physicians:** internal medicine, rheumatology and paediatrics. **Nurses**	Brochure concerning the following therapeutic indications: rheumatoid arthritis, giant cell arteritis, polyarticular juvenile idiopathic arthritis and systemic juvenile idiopathic arthritis.
	Patients	Brochure for patients with polyarticular juvenile idiopathic arthritis. Alert card. 22-08-2018

Compiled by Magda Pedro

What do they mean?

ADR	Adverse Drug Reaction
EMA	European Medicines Agency
MA	Marketing Authorization
PIL	Patient Information Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee (EMA)
SmPC	Summary of Product Characteristics