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Tofacitinib (Xeljanz®)
new recommendations for use

Quick Read
In light of evidence of an increased, dose-dependent risk of deep vein thrombosis and serious venous thromboembolic phenomena, as well as increased mortality associated with cardiovascular events, infections and malignant neoplasms, recommendations for use of tofacitinib have been reviewed.

Tofacitinib is a potent selective Janus kinase (JAK) inhibitor, especially JAK 1, 2 and 3. JAK inhibition reduces signalling of interleukins and interferons, thus modulating immune and inflammatory responses. Tofacitinib is indicated, in association with methotrexate, in the treatment of adults with moderate to severe rheumatoid arthritis, active psoriatic arthritis and, in monotherapy, in the treatment of adult patients with moderately to severely active ulcerative colitis.

Following marketing authorization, a study on the cardiovascular safety of Xeljanz® was required. In this study Xeljanz® 5 mg and 10 mg bid was to be compared with a tumour necrosis factor inhibitor (TNFi). The study population included patients older than 50 years with rheumatoid arthritis and at least one additional cardiovascular risk factor (e.g., smoking, elevated arterial blood pressure, hypercholesterolaemia, diabetes mellitus, a family history of myocardial infarction and coronary disease).

In a preliminary assessment of the study's results, comparatively to TNFi, Xeljanz® was associated with an increased and dose-dependent risk of deep venous thrombosis and serious venous thromboembolism (VTE), including cases of pulmonary embolism, some of which fatal. Moreover, increased mortality was observed, mostly due to cardiovascular events, infections and malignant neoplasms.

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INDEX CARD

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▶ *Cont'd*

Those findings prompted an assessment by the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) from which new recommendations for the use of Xeljanz® resulted, in order to minimize the risk of VTE and infections, as already previously communicated by **Infarmed**. The sections on **posology and warnings** of the Summary of the Product's Characteristics (**SPC**) and Information Leaflet have been updated accordingly. The following recommendations are highlighted:

- Irrespective of indication and dosage, Xeljanz® should be **used with caution** in patients with **known risk factors of VTE** (major surgery, immobilization, myocardial infarction in the preceding 3 months, heart failure, use of combined hormonal contraceptives or hormonal replacement therapy, hereditary coagulation disorder, malignant neoplasm; additional risk factors: age, obesity (BMI ≥ 30), diabetes, hypertension, smoking).
- In the treatment of **rheumatoid arthritis the recommended dose should not be exceeded**: 5 mg bid (film-coated tablets) or 11 mg qd (sustained release tablets).
- In the treatment of **psoriatic arthritis the recommended dose should not be exceeded**: 5 mg bid.
- **Maintenance treatment** (with the 10 mg bid dosage) **is not recommended** for patients with **ulcerative colitis** who have **known risk factors of VTE** (unless there is no therapeutic alternative).
- Treatment of elderly patients should be considered only when there is no adequate therapeutic alternative, since patients **older than 65 years** are at **increased risk of serious infections and associated mortality**.

Patients should be periodically evaluated for signs and symptoms of VTE and tofacitinib stopped should VTE be suspected, irrespective of indication or dosage.

A Dear Healthcare Professional Communication (**DHPC**) has been disseminated and **Educational Materials** updated, including:

– Patient alert card (to be handed out by the physician)

– Guide for the prescribing physician

– Prescriber's start of treatment checklist

– Prescriber's treatment maintenance checklist

Carolina Maia Santos, Constança Oliveira

Portal **RAM**
Notificação de Reações Adversas a Medicamentos

Report an adverse drug reaction here.
Find answers to your questions about the ADR Portal here.

ADRs in the Literature
False penicillin allergy in hospitalized patients

The authors of this short study published as a Letter to the Editor of Acta Médica Portuguesa started from literature evidence pointing to a prevalence of true penicillin allergy significantly lower than reported. Among other problems, a false diagnosis of penicillin allergy can prompt the use of alternative second-line antimicrobials with the attending risk of bacterial resistance and even lower efficacy.

The study was undertaken in an internal medicine department of a major hospital in Portugal. It included 680 admitted patients, in 40 of which a history of "penicillin allergy" was identified. Half of them reported urticaria, anaphylaxis or rash, while the other half could not recall the clinical manifestations they may have had. Sixty-five percent reported an allergy episode more than 30 years before.

Of **16 cases** in which full clinical and laboratory workups could be conducted, **allergy** was confirmed in **only two**.

The authors underscore the relevance of **confirming** a history of penicillin allergy as soon as possible. On the one hand, other adverse drug reactions ("intolerance") and true allergy are often mixed up. On the other, many individuals lose their hypersensitivity with time.

- ***Cardoso BK et al. Penicillin Allergy: The Impact of a False Diagnosis. Cartas ao Editor, Acta Med Port 2019 Nov;32(11):734–735.***

Educational Materials published on the Infomed product information webpage
Click on the links.

INN Medicinal product	Target	Comunication Online publication date
Atezolizumab Tecentriq	**Healthcare professionals:** pneumologists, urologists, oncologists, radio-oncologists, gynaecologists and internists treating patients with breast, lung and/or bladder cancer; nurses	Guide on adverse immune reactions
	Patients	Alert Card 28-01-2020
Darvadstrocel Alofisel	**Healthcare professionals:** surgeons, gastroenterologists; nurses	Administration method Administration method (video)
	Physicians: surgeons and gastroenterologists	Potential microbial contamination and steps in case of positive culture
	Pharmacists: hospital	Instructions for reception and storage 21-01-2020
Pegvaliase Palynziq	**Healthcare professionals:** who prescribe the medicine or are involved in the treatment of patients with phenylketonuria	Guide for healthcare professionals
	Patients and trained observers	Guide for patients and trained observers
	Patients	Alert Card 06-01-2020
Sildenafil Revatio 0,8 mg/ml Solução injetável	**Healthcare professionals:** with experience in the treatment and/or control of patients with pulmonary arterial hypertension and involved in therapy with this medicine	Brochure on risk of hypotension Patient data form 07-01-2020

Compiled by Patrícia Catalão

Communications to Healthcare Professionals published on the Infomed product information webpage

Click on the links.

INN Medicinal product	Target	Comunication Online publication date
Alemtuzumab Lemtrada	**Physicians:** neurologists, heads of hospital neurology dpts, Portuguese Neurology Society **Nurses:** at neurology dpts **Pharmacists:** directors of hospital pharmacy services	Indication restriction, additional contraindications and risk minimization measures 23-01-2020
Anidulafungin Ecalta	**Pharmacists:** hospital	Infusion solution must not be frozen 24-01-2020
Etonogestrel Implanon NXT	**Physicians:** heads of family health centres, gynaecologists, family planning	Update of instructions for insertion and removal to minimize risk of neurovascular injury and implant migration 21-01-2020
Levothyroxine sodium Eutirox	**Physicians:** endocrinology, general/family medicine, internal medicine, paediatrics, gynaecology/obstetrics, cardiology **Pharmacists:** community and hospital	Patient monitoring during transition to new formula 03-01-2020
Ingenol mebutate Picato	**Physicians:** dermatology and general/family medicine **Pharmacists:** community	Marketing authorization suspension on account of risk of malignant skin neoplasms 27-01-2020
Metotrexate Metotrexato Accord Ledertrexato Fauldexato Metex Metex PEN Metotrexato Teva	**Physicians:** oncology, rheumatology, internal medicine (autoimmune conditions) and dermatology **Pharmacists:** community and hospital	Recommendations to prevent potentially fatal dosing errors when treating autoimmune conditions 13-01-2020

Compiled by Patrícia Catalão