5 July 2021[1]
EMA/PRAC/333370/2021
Pharmacovigilance Risk Assessment Committee (PRAC)

# New product information wording – Extracts from PRAC recommendations on signals – Part 2

Adopted at the 7-10 June 2021 PRAC

The product information wording in this document is extracted from the document entitled 'PRAC recommendations on signals' which contains the whole text of the PRAC recommendations for product information update, as well as some general guidance on the handling of signals. It can be found ***here*** (in English only).

New text to be added to the product information is underlined. Current text to be deleted is ~~struck through~~.

## 1. Ceftriaxone – Hepatitis (EPITT no 19603)

**Summary of product characteristics**

4.8. Undesirable effects

Under SOC Hepatobiliary disorders with frequency "Not known"

Hepatitis[c]

Hepatitis cholestatic[b,c]

[b] See section 4.4

[c] Usually reversible upon discontinuation of ceftriaxone

**Package leaflet**

4. Possible side effects

Under frequency "Not known"

Problems with gallbladder and/or liver, which may cause pain, nausea, vomiting, ~~feeling sick, and being sick,~~ yellowing of the skin, itching, unusually dark urine and clay-coloured stools.

[1] Expected publication date. The actual publication date can be checked on the webpage dedicated to PRAC recommendations on safety signals.

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# 2. Tofacitinib – Major adverse cardiovascular events (MACE) and malignancies excluding non-melanoma skin cancer (NMSC) from a clinical trial (EPITT no 19382)

**Summary of product characteristics**

4.2. Posology and method of administration

*Elderly*
No dose adjustment is required in patients aged 65 years and older. There are limited data in patients aged 75 years and older. See section 4.4 for Use in patients over 65 years of age.

4.4. Special warnings and precautions for use

Use in patients over 65 years of age

Considering the increased risk of serious infections, myocardial infarction, and malignancies with tofacitinib in patients over 65 years of age, tofacitinib should only be used in these patients if no suitable treatment alternatives are available (see further details below in section 4.4 and section 5.1).

The risks and benefits of treatment should be considered prior to initiating tofacitinib in patients:
[…]
- ~~who are over 65 years of age~~

As there is a higher incidence of infections in the elderly and in the diabetic populations in general, caution should be used when treating the elderly and patients with diabetes (see section 4.8). In patients over 65 years of age tofacitinib should only be ~~considered~~ used if no suitable ~~alternative~~ treatment alternatives are available (see section 5.1).

Viral reactivation
[…]

Major adverse cardiovascular events (including myocardial infarction)

Major adverse cardiovascular events (MACE) have been observed in patients taking tofacitinib.

In a randomised post authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, an increased incidence of myocardial infarctions was observed with tofacitinib compared to TNF inhibitors (see sections 4.8 and 5.1). In patients over 65 years of age, patients who are current or past smokers, and patients with other cardiovascular risk factors, tofacitinib should only be used if no suitable treatment alternatives are available.

Malignancy and lymphoproliferative disorder
~~The risks and benefits of tofacitinib treatment should be considered prior to initiating therapy in patients with current or a history of malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing tofacitinib in patients who develop a malignancy. The possibility exists for tofacitinib to affect host defences against malignancies.~~

~~Lymphomas have been observed in patients treated with tofacitinib. Patients with RA, particularly those with highly active disease may be at a higher risk (up to several fold) than the general population for the development of lymphoma. The effect of tofacitinib on the development of lymphoma is uncertain.~~

~~Other malignancies were observed in clinical studies and the post-marketing setting, including, but not limited to, lung cancer, breast cancer, melanoma, prostate cancer, and pancreatic cancer.~~

~~The effect of tofacitinib on the development and course of malignancies is not known.~~

Tofacitinib may affect host defences against malignancies.

In a randomised post authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, an increased incidence of malignancies excluding NMSC, particularly lung cancer and lymphoma, was observed with tofacitinib compared to TNF inhibitors(see sections 4.8 and 5.1).

Lung cancers and lymphoma in patients treated with tofacitinib have also been observed in other clinical studies and in the post marketing setting.

Other malignancies in patients treated with tofacitinib were observed in clinical studies and the post-marketing setting, including, but not limited to, breast cancer, melanoma, prostate cancer, and pancreatic cancer.

In patients over 65 years of age, patients who are current or past smokers, and patients with other malignancy risk factors (e.g. current malignancy or history of malignancy other than a successfully treated non-melanoma skin cancer) tofacitinib should only be used if no suitable treatment alternatives are available.

~~*Cardiovascular risk*~~

~~RA and PsA patients have an increased risk for cardiovascular disorders. Patients treated with tofacitinib should have risk factors (e.g., hypertension, hyperlipidaemia) managed as part of usual standard of care~~

4.8. Undesirable effects

The most commonly reported adverse reactions during the first 3 months of the double-blind, placebo or MTX controlled clinical trials were headache, upper respiratory tract infections, nasopharyngitis, diarrhoea, nausea and hypertension (see Table 6, Adverse Drug Reactions [ADRs] based on all study durations).

SOC: Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Frequency uncommon: Lung cancer
Frequency rare: Lymphoma

SOC: Cardiac disorders
Frequency uncommon: Myocardial infarction

*Rheumatoid arthritis*
In a large, randomised post-authorisation safety surveillance study of rheumatoid arthritis patients who were 50 years of age and older and had at least one additional cardiovascular (CV) risk factor, VTE was observed at an increased and dose-dependent incidence in patients treated with tofacitinib compared to TNF inhibitors. The majority of these events were serious and some resulted in death. In an interim safety analysis**,** the incidence rates (95% CI) for PE for tofacitinib 10 mg twice daily, tofacitinib 5 mg twice daily, and TNF inhibitors were 0.54 (0.32-0.87), 0.27 (0.12-0.52), and 0.09 (0.02-0.26) patients with events per 100 patient-years, respectively. Compared with TNF inhibitors, the hazard ratio (HR) for PE was 5.96 (1.75-20.33) and 2.99 (0.81-11.06) for tofacitinib 10 mg twice daily and tofacitinib 5 mg twice daily, respectively (see section 5.1).

In a subgroup analysis in patients with VTE risk factors in the above-mentioned interim analysis of the study, the risk for PE was further increased. Compared with TNF inhibitors, the HR for PE was 9.14 (2.11-39.56) for tofacitinib 10 mg twice daily and 3.92 (0.83-18.48) for tofacitinib 5 mg twice daily.

*Myocardial infarction*

*Rheumatoid arthritis*
In a large (N=4,362) randomised post-authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, the incidence rates (95% CI) for non-fatal myocardial infarction for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice

daily, and TNF inhibitors were 0.37 (0.22, 0.57), 0.33 (0.19, 0.53), and 0.16 (0.07, 0.31) patients with events per 100 patient-years, respectively. Few fatal myocardial infarctions were reported with rates similar in patients treated with tofacitinib compared to TNF inhibitors (see sections 4.4 and 5.1). The study required at least 1500 patients to be followed for 3 years.

*Malignancies excluding NMSC*

*Rheumatoid arthritis*
In a large (N=4,362) randomised post-authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, the incidence rates (95% CI) for lung cancer for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitors were 0.23 (0.12, 0.40), 0.32 (0.18, 0.51), and 0.13 (0.05, 0.26) patients with events per 100 patient-years, respectively (see sections 4.4 and 5.1). The study required at least 1500 patients to be followed for 3 years.

The incidence rates (95% CI) for lymphoma for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitors were 0.07 (0.02, 0.18), 0.11 (0.04, 0.24), and 0.02 (0.00, 0.10) patients with events per 100 patient-years, respectively (see sections 4.4 and 5.1).

5.1. Pharmacodynamic properties

Long-term controlled safety data

Study ORAL Surveillance (A3921133) ~~is~~ was a large (N=4362), ~~ongoing~~, randomised active-controlled post-authorisation safety surveillance study of rheumatoid arthritis patients who were ~~at least~~ 50 years of age and older and had at least one additional cardiovascular risk factor (CV risk factors defined as: current cigarette smoker, diagnosis of hypertension, diabetes mellitus, family history of premature coronary heart disease, history of coronary artery disease including a history of revascularization procedure, coronary artery bypass grafting, myocardial infarction, cardiac arrest, unstable angina, acute coronary syndrome, and presence of extra-articular disease associated with RA, e.g. nodules, Sjögren's syndrome, anemia of chronic disease, pulmonary manifestations). Patients were required to be on a stable dose of methotrexate at study entry; dose adjustment was permitted during the study.

Patients were randomised to open-label tofacitinib 10 mg twice daily, tofacitinib 5 mg twice daily, or a TNF inhibitor (TNF inhibitor was either etanercept 50 mg once weekly or adalimumab 40 mg every other week) in a 1:1:1 ratio. The co-primary endpoints ~~are~~ were adjudicated malignancies excluding NMSC and adjudicated major adverse cardiovascular events (MACE); cumulative incidence and statistical assessment of endpoints ~~are~~ were blinded. The study ~~is~~ was an event-powered study that also required at least 1500 patients to be followed for 3 years. The study treatment of tofacitinib 10 mg twice daily ~~has been~~ was stopped and patients were switched to 5 mg twice daily because of a dose-dependent signal of venous thromboembolic events (VTE). For patients in the tofacitinib 10 mg twice daily treatment arm, the data collected before and after the dose switch were analysed in their originally randomised treatment group.

The study did not meet the non-inferiority criterion for the primary comparison of the combined tofacitinib doses to TNF inhibitor since the upper limit of the 95% CI for HR exceeded the pre-specified non-inferiority criterion of 1.8 for adjudicated MACE and adjudicated malignancies excluding NMSC. Final results are provided below for MACE, myocardial infarction, malignancies excluding NMSC, lung cancer and lymphoma for each randomised treatment arm. Interim safety analysis (2019) results are provided for VTE, serious infections, and mortality.

*MACE (including myocardial infarction)*

An increase in non-fatal myocardial infarction was observed in patients treated with tofacitinib compared to TNF inhibitor.

Table 12: Incidence rate and hazard ratio for MACE and myocardial infarction

| | ***Tofacitinib 5 mg twice daily*** | ***Tofacitinib 10 mg twice daily[a]*** | ***All Tofacitinib[b]*** | ***TNF inhibitor (TNFi)*** |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| ***MACE[c]*** | | | | |
| *IR (95% CI) per 100 PY* | *0.91 (0.67, 1.21)* | *1.05 (0.78, 1.38)* | *0.98 (0.79, 1.19)* | *0.73 (0.52, 1.01)* |
| *HR (95% CI) vs TNFi* | *1.24 (0.81, 1.91)* | *1.43 (0.94, 2.18)* | *1.33 (0.91, 1.94)* | |
| ***Fatal MI[c]*** | | | | |
| *IR (95% CI) per 100 PY* | *0.00 (0.00, 0.07)* | *0.06 (0.01, 0.18)* | *0.03 (0.01, 0.09)* | *0.06 (0.01, 0.17)* |
| *HR (95% CI) vs TNFi* | *0.00 (0.00, Inf)* | *1.03 (0.21, 5.11)* | *0.50 (0.10, 2.49)* | |
| ***Non-fatal MI[c]*** | | | | |
| *IR (95% CI) per 100 PY* | *0.37 (0.22, 0.57)* | *0.33 (0.19, 0.53)* | *0.35 (0.24, 0.48)* | *0.16 (0.07, 0.31)* |
| *HR (95% CI) vs TNFi* | *2.32 (1.02, 5.30)* | *2.08 (0.89, 4.86)* | *2.20 (1.02, 4.75)* | |

*[a] The tofacitinib 10 mg twice daily treatment group includes data from patients that were switched from tofacitinib 10 mg twice daily to tofacitinib 5 mg twice daily as a result of a study modification.*
*[b] Combined tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily.*
*[c] Based on events occurring on treatment or within 60 days of treatment discontinuation.*
*Abbreviations: MACE = major adverse cardiovascular events, MI = myocardial infarction, TNF = tumour necrosis factor, IR = incidence rate, HR = hazard ratio, CI = confidence interval, PY = patient years, Inf = infinity*

The following predictive factors for development of MI (fatal and non-fatal) were identified using a multivariate Cox model with backward selection: age ≥ 65 years, male, current or past smoking, history of diabetes, and history of coronary artery disease (which includes myocardial infarction, coronary heart disease, stable angina pectoris, or coronary artery procedures) (see section 4.4 and 4.8).

*Malignancies*

An increase in malignancies excluding NMSC, particularly lung cancer and lymphoma, was observed in patients treated with tofacitinib compared to TNF inhibitor.

Table 13: Incidence rate and hazard ratio for malignancies excluding NMSC[a]

| | ***Tofacitinib 5 mg twice daily*** | ***Tofacitinib 10 mg twice daily[b]*** | ***All Tofacitinib[c]*** | ***TNF inhibitor (TNFi)*** |
|---|---|---|---|---|
| ***Malignancies excluding NMSC*** | | | | |
| *IR (95% CI) per 100 PY* | *1.13 (0.87, 1.45)* | *1.13 (0.86, 1.45)* | *1.13 (0.94, 1.35)* | *0.77 (0.55, 1.04)* |
| *HR (95% CI) vs TNFi* | *1.47 (1.00, 2.18)* | *1.48 (1.00, 2.19)* | *1.48 (1.04, 2.09)* | |
| ***Lung cancer*** | | | | |
| *IR (95% CI) per 100 PY* | *0.23 (0.12, 0.40)* | *0.32 (0.18, 0.51)* | *0.28 (0.19, 0.39)* | *0.13 (0.05, 0.26)* |
| *HR (95% CI) vs TNFi* | *1.84 (0.74, 4.62)* | *2.50 (1.04, 6.02)* | *2.17 (0.95, 4.93)* | |
| ***Lymphoma*** | | | | |
| *IR (95% CI) per 100 PY* | *0.07 (0.02, 0.18)* | *0.11 (0.04, 0.24)* | *0.09 (0.04, 0.17)* | *0.02 (0.00, 0.10)* |
| *HR (95% CI) vs TNFi* | *3.99 (0.45, 35.70)* | *6.24 (0.75, 51.86)* | *5.09 (0.65, 39.78)* | |

*[a] Based on events occurring on treatment or after treatment discontinuation up to the end of the study*
*[b] The tofacitinib 10 mg twice daily treatment group includes data from patients that were switched from tofacitinib 10 mg twice daily to tofacitinib 5 mg twice daily as a result of a study modification.*
*[c] Combined tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily.*
*Abbreviations: NMSC = non melanoma skin cancer, TNF = tumour necrosis factor, IR = incidence rate, HR = hazard ratio, CI = confidence interval, PY = patient years*

The following predictive factors for development of malignancies excluding NMSC were identified using a Multivariate Cox model with backward selection: age ≥ 65 years and current or past smoking (see section 4.4 and 4.8).

*Serious infections*
In an interim analysis, fFor non-fatal serious infections, the incidence rates (95% CI) per 100 patient-years were 3.51 (2.93-4.16), 3.35 (2.78-4.01), and 2.79 (2.28-3.39), for tofacitinib 10 mg and 5 mg

twice daily and TNF inhibitors, respectively. The risk of serious (fatal and non-fatal) infections was further increased in patients over 65 years of age, as compared to younger patients in study A3921133.

**Package leaflet**

2. What you need to know before you are administered Xeljanz

Warnings and precautions

Talk to your doctor or pharmacist before taking XELJANZ:

[…]
- if you are older than 65 years, if you have ever had any type of cancer, and also if you are a current or past smoker. XELJANZ may increase your risk of certain cancers. White blood cell cancer, lung cancer ~~Lymphoma~~ and other cancers (such as ~~lung~~ breast, melanoma, prostate and pancreatic) have been reported in patients treated with XELJANZ. If you develop cancer while taking XELJANZ your doctor will review whether to stop XELJANZ treatment.

[…]
- if you have heart problems, high blood pressure, high cholesterol, and also if you are a current or past smoker.

There have been reports of patients treated with XELJANZ who have developed blood clots in the lungs or veins. Your doctor will evaluate your risk to develop blood clots in the lungs or veins and determine if XELJANZ is appropriate for you. If you have already had problems on developing blood clots in lungs and veins or have an increased risk for developing this (for example: if you are seriously overweight, if you have cancer, heart problems, diabetes, experienced a heart attack (within previous 3 months), recent major surgery, if you use hormonal contraceptives\hormonal replacement therapy, if a coagulation defect is identified in you or your close relatives), if you are of older age, or if you smoke currently or in the past, your doctor may decide that XELJANZ is not suitable for you.

There have been reports of patients treated with XELJANZ who have had a heart problem, including heart attack. Your doctor will evaluate your risk to develop a heart problem and determine if XELJANZ is appropriate for you. Talk to your doctor straight away if you develop signs and symptoms of a heart attack including severe chest pain or tightness (that may spread to arms, jaw, neck, back), shortness of breath, cold sweat, light headedness or sudden dizziness.

Elderly
[…]

Patients aged 65 years and older may be at increased risk of infections, heart attack and some types of cancer. Your doctor may decide that XELJANZ is not suitable for you.

4. Possible side effects

Possible serious side effects

[…]
Lung cancer, white blood cell cancer and heart attack have also been reported.

[…]

Signs of a heart attack (uncommon) include
- severe chest pain or tightness (that may spread to arms, jaw, neck, back)
- shortness of breath
- cold sweat

- light headedness or sudden dizziness

Uncommon (may affect up to 1 in 100 people): lung cancer […]

Rare (may affect up to 1 in 1,000 people): blood infection (sepsis), lymphoma (white blood cell cancer) […]