Pfizer Hellas S.A.
243, Messoghion Avenue,
GR-154 51, Neo Psychiko,
Athens, Greece

20-Mar-2021

▼Xeljanz (tofacitinib): Initial clinical trial results of increased risk of major adverse cardiovascular events and malignancies (excluding NMSC) with use of tofacitinib relative to TNF-alpha inhibitors

Dear Healthcare Professional,

Pfizer Europe MA EEIG in agreement with the European Medicines Agency (EMA) and the Medicines Authority would like to inform you of the following:

Summary

- **Preliminary data from a completed clinical trial in rheumatoid arthritis patients (A3921133) suggest a higher risk of major adverse cardiovascular events (MACE) and malignancies (excluding non-melanoma skin cancer (NMSC)) with tofacitinib as compared to patients treated with a TNF-alpha inhibitor.**
- **Keep considering the benefits and risks of tofacitinib when deciding whether to prescribe or continue patients on the medicine. Continue to follow the recommendations in the tofacitinib product information.**
- **Advise patients that they should not stop taking tofacitinib without first consulting their healthcare professional and to talk to their healthcare professional if they have questions or concerns.**
- **Further evaluation of the data from study A3921133 and their potential impact on tofacitinib product information by EMA is currently ongoing and final conclusions and recommendations will be communicated as soon as the evaluation has been completed.**

Background on the safety concern

Tofacitinib is a JAK-inhibitor and indicated as treatment for

- adult patients with moderate to severe rheumatoid arthritis (RA) or active psoriatic arthritis (PsA) in patients who have responded inadequately to, or who are intolerant to one or more disease-modifying antirheumatic drugs.

- adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent.

Long-term safety study A3921133 in patients with RA

Study ORAL surveillance (A3921133) is a large (N=4,362) randomized active-controlled clinical trial to evaluate the safety of tofacitinib at two doses (5 mg twice daily and 10 mg twice daily) versus a tumor necrosis factor alpha inhibitor (TNF-alpha inhibitors) in subjects with RA who were 50 years of age or older and had at least one additional cardiovascular risk factor (defined in the protocol as current cigarette smoker, high blood pressure, high-density lipoprotein [HDL] <40 mg/dL, diabetes mellitus, history of coronary artery disease, family history of premature coronary heart disease, extraarticular RA disease), some of which are also known risk factors for malignancy.

The co-primary endpoints of this study were adjudicated MACE and adjudicated malignancies (excluding NMSC). The study is an event-powered study that also requires at least 1500 patients to be followed for 3 years. Prespecified non-inferiority criteria were not met for these co-primary endpoints and the clinical trial could not demonstrate tofacitinib is non-inferior to ("not worse than") TNF-alpha inhibitors. Results suggest that these risks are associated with both approved dosage/dosing regimens (5 mg twice daily, and 10 mg twice daily which is approved only in UC).

The primary analyses included 135 subjects with adjudicated MACE and 164 subjects with adjudicated malignancies (excluding NMSC). The most frequently reported MACE was myocardial infarction. The most frequently reported malignancy (excluding NMSC) was lung cancer. In those subjects with a higher prevalence of known risk factors for MACE and malignancy (e.g., older age, smoking), a higher occurrence of events was seen across all treatment groups.

*Adjudicated MACE**

	Tofacitinib 5 mg BID	**Tofacitinib 10 mg BID****	**Tofacitinib Doses Combined**	**TNF-alpha inhibitors**
Total number of subjects	1455	1456	2911	1451
Number of subjects with first event within the risk period*** (%)	47 (3.23)	51 (3.50)	98 (3.37)	37 (2.55)
Person-years	5166.32	4871.96	10038.28	5045.27
IR (95% CI) (number of subjects with event/100 person-years)	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) for tofacitinib vs TNF-alpha inhibitors	1.24 (0.81, 1.91)	1.43 (0.94, 2.18)	1.33 (0.91, 1.94)****	

(*) Based on Cox proportional hazard model
(**)The 10 mg BID treatment group includes patients that were switched from 10 mg BID to 5 mg BID as a result of a study modification in February 2019.
(***) The risk period was from start of therapy up to 60 days past last dose.
(****) The non-inferiority criterion was not met for the primary comparison of the combined tofacitinib doses to TNF-alpha inhibitors since the upper limit of the 95% CI exceeded the pre-specified non-inferiority criterion of 1.8, ie, 1.94 >1.8.

*Adjudicated Malignancies Excluding NMSC**

	Tofacitinib 5 mg BID	**Tofacitinib 10 mg BID****	**Tofacitinib Doses Combined**	**TNF-alpha inhibitors**
Total number of subjects	1455	1456	2911	1451
Number of subjects with first event within the risk period*** (%)	62 (4.26)	60 (4.12)	122 (4.19)	42 (2.89)
Person-years	5491.48	5311.71	10803.19	5482.30
IR (95% CI) (number of subjects with event/100 person-years)	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) for tofacitinib vs TNF-alpha inhibitors	1.47 (1.00, 2.18)	1.48 (1.00, 2.19)	1.48 (1.04, 2.09)****	

(*) Based on Cox proportional hazard model
(**)The 10 mg BID treatment group includes patients that were switched from 10 mg BID to 5 mg BID as a result of a study modification in February 2019.
(***) The risk period included all available follow-up regardless of treatment exposure.
(****) The non-inferiority criterion was not met for the primary comparison of the combined tofacitinib doses to TNF-alpha inhibitors since the upper limit of the 95% CI exceeded the pre-specified non-inferiority criterion of 1.8, ie, 2.09 >1.8.

Further evaluation of the data from study A3921133 and their potential impact on tofacitinib product information by EMA is currently ongoing. The final conclusions and recommendations will be communicated as soon as the evaluation has been completed.

Call for reporting

Healthcare professionals are reminded to continue to report suspected adverse reactions associated with Xeljanz ▼in accordance with the National spontaneous reporting system. Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and sent to ADR reporting/Post-Licensing Directorate/Medicines Authority, Sir Temi Zammit Buildings, Malta Life Sciences Park, San Gwann, Malta, or sent by email to: Postlicensing.medicinesauthority@gov.mt

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

Company contact point

Pfizer Medical Information at
https://www.pfizer.com/products/product-contact-information
Also, please contact Pfizer Hellas S.A. Medical Information at +30 210 67 85 800.
Pfizer Hellas Pharmacovigilance Department contact details:
+30 210 6785908 and +30 210 6785808 (24-hour line).
Local Representative: Vivian Corporation Ltd.: Tel. +00356 22588600.

Sincerely,
For Pfizer Hellas S.A.,

Damianos Menegas MD, PhD
Medical Director
Greece, Cyprus, Malta