This English version is intended to be a reference material for the convenience of users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

Summary of Investigation Results

Tofacitinib citrate

October 12, 2021

Non-proprietary name

Tofacitinib citrate

Branded name (Marketing authorization holder)

Xeljanz Tablets 5 mg (Pfizer Japan Inc.)

Indications

Rheumatoid arthritis in patients who have not adequately responded to conventional treatments

Remission induction and maintenance therapy for moderate to severe ulcerative colitis (only for patients who have not adequately responded to conventional treatments)

Summary of revisions

1. The language indicating that the relationship with this drug is not clear should be removed from the statement regarding malignancy in the WARNING section.
2. “Cardiovascular events such as myocardial infarction” should be added to the precaution regarding patients with risk factors of cardiovascular events in the PRECAUTIONS CONCERNING INDICATIONS section.
3. In the precaution regarding malignancy in the IMPORTANT PRECAUTIONS section, the language indicating that the relationship with this drug is not clear should be revised to language indicating a trend toward a higher incidence for the event found with this drug in the overseas clinical study compared with TNF inhibitors.
4. “Cardiovascular events such as myocardial infarction” should be added to the statement under “Patients with risk factors of cardiovascular events” in the PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS

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section and the results of the overseas clinical study (interim analysis) in such patients should be updated with the final analysis results.

5. "Cardiovascular events" and "malignancy" should be added to the Clinically Significant Adverse Reactions section.
6. The results of the clinical study regarding malignancy should be removed in the Information Based on Clinical Uses, OTHER PRECAUTIONS section.
7. The results of the overseas clinical study in patients with risk factors of cardiovascular events should be added to the CLINICAL STUDIES section.

Investigation results and background of the revision

In view of the final analysis of the overseas clinical study (A3921133 Study) in patients with rheumatoid arthritis who were 50 years and older and had risk factors of cardiovascular events in which the non-inferiority of the group that received this drug to the TNF inhibitor group was not confirmed for the co-primary endpoints of the incidence rates of Major Adverse Cardiovascular Events (MACE) and Malignancy (excluding non-melanoma skin cancer), the necessity of revising the Precautions in the package insert was discussed and MHLW/PMDA in consultation with expert advisors concluded that the following revisions were necessary.

- Given the trend toward a higher risk of both cardiovascular events and malignancy indicated in the study with this drug compared with TNF inhibitors, the two events would be listed as Clinically Significant Adverse Reactions for precaution. Myocardial infarction would be noted as an example considering the incidences of specific events included in the major adverse cardiovascular events in the study.
- Language concerning cardiovascular events would be added to the current precaution for "Patients with risk factors of cardiovascular events."
- Among the current description regarding malignancy, the language concerning the relationship with this drug, etc. would be revised and the results of the clinical studies included in the OTHER PRECAUTIONS section would be removed.
- The current information regarding the study (results of the interim analysis) would be updated with the results of its final analysis, which has recently become available.

Of note, regarding other Janus kinase (JAK) inhibitors (baricitinib, peficitinib hydrobromide,

upadacitinib hydrate, filgotinib maleate), which have been authorized for similar indications and have comparable safety profiles to this drug, there have been no findings on the onset mechanism, etc. to indicate that either cardiovascular events or malignancy is a common risk among the JAK inhibitors. Therefore, it was considered difficult to extrapolate the results of the clinical study to other JAK inhibitors. MHLW/PMDA concluded that similar revisions of Precautions in their package inserts were not necessary at this time.

Number of cases and patient mortalities reported in Japan during the previous 3 fiscal years

Cases involving cardiovascular events

A total of 22 cases have been reported to date (including 5 cases for which a causal relationship between the drug and event was reasonably possible).

A total of 7 patient mortalities have been reported to date. (A causal relationship between the drug and death subsequent to the event could not be established for any of these cases.)

Cases involving malignancy*

A total of 154 cases have been reported to date.

A total of 18 patient mortalities have been reported to date.

*The possibility of a causal relationship with this drug was not evaluated in these cases.

The expert advisors present at the Expert Discussion regarding the current investigation were nominated based on their conflict of interest declarations concerning the relevant products, pursuant to the “Rules for Convening Expert Discussions, etc., by the Pharmaceuticals and Medical Devices Agency” (PMDA Administrative Rule No. 20-8, dated December 25, 2008).