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Revision of Precautions

Tofacitinib citrate

October 12, 2021

Therapeutic category

Agents affecting metabolism, n.e.c. (not elsewhere classified)

Non-proprietary name

Tofacitinib citrate

Safety measure

Precautions should be revised in the package insert.

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Revision in line with the Instructions for Electronic Package Inserts of Prescription Drugs, etc. PSEHB Notification No. 0611-1 by the Director of Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated June 11, 2021 (New instructions): Revised language is underlined.

Current	Revised
1. WARNINGS New onset or worsening of serious infection by tuberculosis, pneumonia, sepsis, or virus infection has been reported following administration of this drug. Onset of malignancy has also been reported following administration of this drug although the relationship with this drug is not clear. Including the fact that this drug is not an agent to completely cure a disease, such information should be fully made known to patients and their understanding should be ensured before this drug is administered. In addition, this drug should be administered only if the potential therapeutic benefits are considered to outweigh the potential risks. Serious adverse reactions may also occur and take a fatal course following administration of this drug. This drug should be used in the healthcare facilities and by the physicians that are highly capable of responding to emergencies, and patients should be warned to contact their physicians immediately if such adverse reactions occur following administration of this drug.	1. WARNINGS New onset or worsening of serious infection by tuberculosis, pneumonia, sepsis, or virus infection as well as onset of malignancy has been reported following administration of this drug. Including the fact that this drug is not an agent to completely cure a disease, such information should be fully made known to patients and their understanding should be ensured before this drug is administered. In addition, this drug should be administered only if the potential therapeutic benefits are considered to outweigh the potential risks. Serious adverse reactions may also occur and take a fatal course following administration of this drug. This drug should be used in the healthcare facilities and by the physicians that are highly capable of responding to emergencies, and patients should be warned to contact their physicians immediately if such adverse reactions occur following administration of this drug.
5. PRECAUTIONS CONCERNING INDICATIONS <Common to all indications> When administration of this drug is considered in patients with risk	5. PRECAUTIONS CONCERNING INDICATIONS <Common to all indications> When administration of this drug is considered in patients with risk

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factors of cardiovascular events, alternative treatments should be considered first, since venous thromboembolism may occur.	factors of cardiovascular events, alternative treatments should be considered first, since cardiovascular events such as myocardial infarction or venous thromboembolism may occur.
8. IMPORTANT PRECAUTIONS Onset of malignancy such as malignant lymphoma and solid tumor has been reported. Although the causal relationship with this drug is not clear, caution should be exercised for the onset of malignancy.	8. IMPORTANT PRECAUTIONS Onset of malignancy such as malignant lymphoma and solid tumor has been reported. Also there has been a report that a trend toward a higher incidence of malignancy was observed with this drug compared with TNF inhibitors in an overseas clinical study. Caution should be exercised for the onset of malignancy.
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS 9.1 Patients with Complication or History of Diseases, etc. Patients with risk factors of cardiovascular events Alternative treatments should be considered first. In particular, the necessity of administration of this drug 10 mg twice daily should be determined with caution. When this drug is administered, the onset of signs and symptoms of venous thromboembolism should be closely monitored. Venous thromboembolism may occur. In an ongoing overseas clinical study in patients with rheumatoid arthritis who are 50 years old or older and have at least 1 risk factor of cardiovascular events (such as smoking, hypertension, diabetes mellitus, and a history of	9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS 9.1 Patients with Complication or History of Diseases, etc. Patients with risk factors of cardiovascular events Alternative treatments should be considered first. In particular, the necessity of administration at 10 mg twice daily should be determined with caution. When this drug is administered, the onset of signs and symptoms of cardiovascular events such as myocardial infarction and venous thromboembolism should be closely monitored. In an overseas clinical study in patients with rheumatoid arthritis who had risk factors of cardiovascular events (such as smoking, hypertension, diabetes mellitus, and a history of coronary artery

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coronary artery disease), it has been reported that a trend toward a higher incidence of pulmonary embolism and deep vein thrombosis was observed in a dose-dependent manner in the groups that received 5 mg or 10 mg of this drug twice daily compared with the TNF inhibitors group, and that the incidence of death including sudden cardiac death tended to be similar between the TNF inhibitors group and the group that received 5 mg of this drug twice daily, while the rate tended to be higher in the group that received 10 mg of this drug twice daily.	disease), a trend toward a higher incidence of cardiovascular events such as myocardial infarction was observed in the groups that received this drug compared with the TNF inhibitors group. A trend toward a higher incidence of venous thromboembolism was also observed with this drug in a dose-dependent manner, and it has been reported that the incidence of death tended to be higher in the group that received 10 mg of this drug twice daily.
11. ADVERSE REACTIONS 11.1 Clinically Significant Adverse Reactions (N/A)	11. ADVERSE REACTIONS 11.1 Clinically Significant Adverse Reactions Cardiovascular events Cardiovascular events such as myocardial infarction may occur. Malignancy
15. OTHER PRECAUTIONS 15.1 Information Based on Clinical Uses <Rheumatoid arthritis> In 5 controlled studies conducted in Japan or overseas for up to 1 year, this drug was administered to 3 030 cases (2 098 patient-years) and placebo to 681 cases (203 patient-years). As a result, malignancy (excluding non-melanoma skin cancer) occurred in 13	15. OTHER PRECAUTIONS 15.1 Information Based on Clinical Uses <Rheumatoid arthritis> (deleted)

cases in the groups that received this drug compared with no cases in the placebo group. The incidence of malignancy (excluding non-melanoma skin cancer) for respective exposure level was 0.55/100 patient-years (95% CI: 0.23 to 1.33, incidence: 0.4% [5/1 216 cases]) in patients with rheumatoid arthritis who received 5 mg of this drug twice daily, and 0.88/100 patient-years (95% CI: 0.44 to 1.76, incidence: 0.7% [8/1 214cases]) in patients with rheumatoid arthritis who received 10 mg of this drug twice daily, the latter higher than the former. In several clinical studies conducted in Japan and overseas, malignancy (excluding non-melanoma skin cancer) occurred in 65 cases in total in the groups that received this drug. The incidence by time to onset is shown in the table. In addition, onset of lymphoma has been reported in patients with rheumatoid arthritis who received this drug. In a clinical study conducted overseas in patients who had undergone renal transplantation, the incidence of EB Virus-related lymphoma was 2.3% (5/218 cases, 4 cases of non-Hodgkin's lymphoma, 1 case of Hodgkin's lymphoma) in patients who received this drug while the incidence of lymphoma was 0% (0/111 cases) in patients who received ciclosporin, both in combination with multiple immunosuppressants. <Ulcerative colitis> In 4 controlled studies conducted in Japan and overseas as well as a long-term treatment study, a total of 7 cases of malignancy	<Ulcerative colitis> (deleted)

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(excluding non-melanoma skin cancer) including 1 case of lymphoma were reported in all dose groups combined. All the 7 cases were observed in the PD (Predominant Dose) 10 mg per dose twice daily group. Non-melanoma skin cancer was reported in 10 cases, including 9 cases in the PD 10 mg per dose, twice daily group. The incidence of non-melanoma skin cancer in the PD 10 mg per dose twice daily group was higher than in the PD 5 mg per dose twice daily group. Likewise, the incidence of non-melanoma skin cancer was higher in the PInd (Post-Induction dose) 10 mg per dose twice daily group than in the PInd 5 mg per dose twice daily group. There was no trend toward an increased incidence of non-melanoma skin cancer in proportion to the treatment duration.	
17. CLINICAL STUDIES (N/A)	17. CLINICAL STUDIES 17.3 Others Overseas post-market clinical study (A3921133 Study) An open-label, randomized, parallel-group, controlled study was conducted in 4 362 foreign patients with rheumatoid arthritis who were 50 years old or older and had at least 1 risk factor of cardiovascular events (such as smoking, hypertension, diabetes mellitus, and a history of coronary artery disease) to investigate the safety following administration of this drug (5 mg or 10 mg twice daily [Note 1)] or TNF inhibitors. The non-inferiority of the groups that received this drug to the TNF

inhibitor group was not confirmed for either the incidence rate of major adverse cardiovascular events [note 2)] (MACE) or the incidence rate of malignancy (excluding non-melanoma skin cancer) as the co-primary endpoints.

Table Incidence rate of Major Adverse Cardiovascular Events (MACE)

	5 mg BID N=1 455	10 mg BID N=1 456	This drug combined N=2 911	TNF inhibitors N=1 451
Incidence rate per 100 patient-years (95% CI)	0.91 (0.67, 1.21)	1.05 (0.78, 1.38)	0.98 (0.79, 1.19)	0.73 (0.52, 1.01)
Hazard ratio (95% CI)	1.24 (0.81, 1.91)	1.43 (0.94, 2.18)	1.33 (0.91, 1.94)[a]	

a: The upper limit of CI 95% for the hazard ratio of the groups of this drug combined to the TNF inhibitors group exceeded the preset non-inferiority margin of 1.8.

Table Incidence rate of Malignancy (excluding non-melanoma skin cancer)

	5 mg BID N=1 455	10 mg BID N=1 456	This drug combined N=2 911	TNF inhibitors N=1 451
Incidence rate per	1.13 (0.87,	1.13 (0.86,	1.13 (0.94,	0.77 (0.55,

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100 patient-years (95% CI)	1.45)	1.45)	1.35)	1.04)
Hazard ratio (95% CI)	1.47 (1.00, 2.18)	1.48 (1.00, 2.19)	1.48 (1.04, 2.09)[b]	

b: The upper limit of CI 95% for the hazard ratio of the groups that received this drug combined to the TNF inhibitors group exceeded the preset non-inferiority margin of 1.8.

The incidence rate of pulmonary embolism, deep vein thrombosis, and total death was as in the table below.

Table Incidence rate of Pulmonary Embolism and Deep Vein Thrombosis

	5 mg BID N=1 455	10 mg BID N=1 456	This drug combined N=2 911	TNF inhibitors N=1 451
Pulmonary embolism	0.17 (0.08, 0.33)	0.50 (0.32, 0.74)	0.33 (0.23, 0.46)	0.06 (0.01, 0.17)
Deep vein thrombosis	0.21 (0.11, 0.38)	0.31 (0.17, 0.51)	0.26 (0.17, 0.38)	0.14 (0.06, 0.29)

Incidence rate per 100 patient-years (95% CI)

Table Incidence rate of Total Death

	5 mg BID N=1 455	10 mg BID N=1 456	This drug combined N=2 911	TNF inhibitors N=1 451
Total death	0.50 (0.33, 0.74)	0.80 (0.57, 1.09)	0.65 (0.50, 0.82)	0.34 (0.20, 0.54)

Incidence rate per 100 patient-years (95% CI)

Note1) The approved dosage and administration of this drug for the indication of rheumatoid arthritis are oral administration of tofacitinib 5 mg twice daily.

Note2) MACE was defined in the study as follows:

· Cardiovascular death: Death due to acute myocardial infarction, sudden cardiac death, death due to heart failure, death due to stroke, death due to cardiovascular procedures, death due to cardiovascular haemorrhage, death due to other cardiovascular causes: Peripheral artery disease.

· Non-fatal myocardial infarction

· Non-fatal stroke of any classification, including reversible focal neurologic defects with imaging evidence of a new cerebral lesion consistent with ischaemia or haemorrhage.