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Report on Investigation Results

June 20, 2019
Pharmaceuticals and Medical Devices Agency

I. Outline of the product

[Branded name]	Feburic Tablets 10 mg, 20 mg, 40 mg
[Nonproprietary name]	Febuxostat
[Marketing authorization holder]	Teijin Pharma Limited
[Indications]	(1) Gout, hyperuricemia, (2) Hyperuricemia associated with chemotherapy
[Dosage and Administration]	(1) The usual initial adult dose is 10 mg of febuxostat administered orally once daily. Subsequently, the dosage should be gradually increased as needed while confirming serum urate concentration. The usual maintenance dose is 40 mg once daily. Dosage should be adjusted as needed according to the patient's condition. The maximum dosage of febuxostat is 60 mg once daily. (2) The usual adult dose is 60 mg of febuxostat administered orally once daily.
[Remarks]	None in particular
[Office responsible for the survey]	Office of Pharmacovigilance I

II. Background of investigation

Febuxostat is a drug that inhibits xanthine oxidase used to treat hyperuricemia, which has been available in 78 countries and regions worldwide including the United States as of May 2019 since it obtained manufacturing and marketing approval in Europe in 2008. In Japan, manufacturing and marketing approval was obtained for the indications for "gout and hyperuricemia" in January 2011 and "hyperuricemia associated with chemotherapy" in May 2016.

In the United States, conducting a post-marketing clinical study (CARES study) to assess cardiovascular risks (CV risks) of febuxostat in patients with gout who have cardiac disease (CVD) was required since a higher incidence of

3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013 Japan
E-mail: safety.info@pmda.go.jp

cardiovascular adverse events was suggested [1] in the febuxostat group compared to the control groups (placebo group or allopurinol group) in the approval review[2] of febuxostat.

The Food and Drug Administration (FDA) issued Drug Safety Communications[3] in November 2017 and announced that they would start a safety assessment of febuxostat since preliminary results from the CARES study showed a higher risk of CV death in the febuxostat group compared to the allopurinol group. Furthermore, the FDA revised the package insert in February 2019 based on the deliberation of the Advisory Committee held in January 2019, established the Boxed Warning section to alert CV deaths and restricted the use of febuxostat to certain patients who have an inadequate response or intolerance to allopurinol (refer to Appendix 1.)

The European Medicine Agency required a clinical study (FAST study) to be conducted by the marketing authorization holder (MAH) of febuxoxtat to assess cardiovascular safety of allopurinol and febuxostat as a post-marketing clinical study to assess CV risks of febuxostat in patients with gout who had cardiac disease since a higher incidence of cardiovascular adverse events was observed in the febuxostat group compared to the allopurinol group in the approval review[4]. The FAST study is ongoing (scheduled to submit a clinical study report by the end of August 2020). The revision of the package insert related to CV risks has not been made as of June 18, 2019 (refer to Appendix 1.).

There was no particularly higher incidence of CV events in the febuxostat group compared to the control groups (placebo group or allopurinol group) in clinical studies[5] conducted in Japan. However, the incidence of CV events was noted to be higher based on foreign clinical studies in the approval reviews in Europe and the United States. Therefore, conducting post-marketing surveillance to collect information on CV risks of febuxostat was required at the initial approval review in Japan (Review Report dated November 8, 2010). A special drug use-results survey was conducted based on the direction (April 2012-June 2018) and the summary report of the survey was submitted to the Pharmaceuticals and Medical

[1] The incidence of primary Anti-Platelet Trialists' Collaboration (APTC) events (composite endpoint of cardiovascular death, non-fatal heart attack, non-fatal cardiac arrest) in the foreign Phase III studies (C02-009 and C02-010) was 1.3 in the febuxostat group, 0.3 in the allopurinol group, 0 in the placebo group as the number of event per 100 patient-years.
[2] Uloric (Takeda Pharmaceuticals America, INC.) approved in February 2009
[3] https://www.fda.gov/media/108760/download (last confirmed June 12, 2019)
[4] Adenuric (Menarini International Operations Luxembourg S.A.) approved in April 2008
[5] Phase II studies (TMX-67-10, TMX-67-18、TMX-67-19）, Phase III studies（TMX-67-12, TMX-67-13）long term trial（TMX-67-11, TMX-67-20）

3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013 Japan
E-mail: safety.info@pmda.go.jp

Devices Agency (PMDA) in May 2019. For the alert related to the CV risks in Japanese package insert, “electrocardiogram abnormal (< 1%)” and “palpitations (frequency unknown)” have been listed in the Other Adverse Reactions section. Moreover, “cardiovascular events” was specified as “important potential risks” in the Risk Management Plan (RMP) developed when a partial change application was approved in May 2016.

In light of the above circumstances both in Japan and overseas, the Pharmaceutical Safety Division, the Pharmaceutical Safety and Environmental Health Bureau, MHLW requested an “investigation on cardiovascular risks of febuxostat” from PMDA on June 5, 2019, and PMDA accordingly conducted the requested investigation and considered the necessity of revision of the package insert.

PMDA has held an Expert Discussion as part of the investigation. The expert advisors for the Expert Discussion were nominated based on their declarations, concerning this product, in accordance with the provisions of “Rules for Convening Expert Discussions, etc., by Pharmaceuticals and Medical Devices Agency” (PMDA Administrative Rule No. 20-8 dated December 25, 2008).

III. Outline of PMDA Investigation

1. Outline of CARES study (N Engl J Med. 2018; 378: 1200-10)

A double-blinded randomized study to compare CV outcome between febuxostat and allopurinol was conducted in gout patients complicated by CVD (target sample size: 3 750 patients per group, total of 7 500 patients).

The dosage of febuxostat was started at 40 mg/day, and 40 mg/day was to be continued if serum urate concentration was below 6 mg/dL or increased to 80 mg/day if serum urate concentration was 6 mg/dL or greater 2 weeks after the initiation. The dosage of allopurinol was started at 300 mg/day in patients with an estimated creatinine clearance of 60 mL/min or greater, and the dosage was to be increased by 100 mg per month until serum urate concentration was below 6 mg/dL or the dosage reached 600 mg/day. The dosage of allopurinol was started at 200 mg/day in patients with an estimated creatinine clearance of 30-60 mL/min, and the dosage was increased by 100 mg per month until serum urate concentration was 6 mg/dL or below, or the dosage reached 400 mg/day.

6 190 patients (febuxostat group: 3 098 patients, allopurinol group: 3 092 patients)[6] were randomized and administered the investigational drug. The final

[6] Patient background (Febuxostat group, Allopurinol group): age ≥ 65 years (48.9%, 51.3%), male (84.1%,

dose of the investigational drugs was: 40 mg/day in 61.0% and 80 mg/day in 39.0% of the patients in the febuxostat group, and 200 mg/day in 21.8%, 300 mg/day in 44.6%, 400 mg/day in 25.2%, 500 mg/day in 4.3%, and 600 mg/day in 4.1% of the patients in the allopurinol group. The mean (range) duration of exposure of the investigational drugs was 728 days (1-2 494 days) in the febuxostat group and 719 days (1-2 529 days) in the allopurinol group. The mean (range) follow-up period was 968 days (1-2 528 days) in the febuxostat group and 942 days (1-2 549 days) in the allopurinol group. Administration of the investigational drugs was discontinued in 56.6% of the subjects during the regimen, and follow-up was discontinued in 45.0% of the subjects during the follow-up period.

Excluding 8 patients who had never received febuxostat or allopurinol, all randomized patients were included in the safety analysis set. The results of the primary endpoint (composite endpoint composed of 4 factors: CV death[7], nonfatal myocardial infarction, nonfatal cerebral stroke, and urgent revascularization for angina unstable) are as shown in Table 1. The hazard ratio (HR) was 1.03 [97% confidence interval (CI): 0.87-1.23]. Since the upper limit of 97% CI of HR was below the predetermined non-inferiority margin 1.3, non-inferiority of febuxostat to allopurinol was suggested regarding the primary endpoint (Modified ITT analysis). The onset of CV death and all-cause death was higher in the febuxostat group compared to the allopurinol group (HR was 1.34 [95%CI: 1.03-1.73] and 1.22 [95%CI: 1.01-1.47], respectively).

83.8%), duration of gout (11.8 years, 11.9 years), serum urate concentration (both groups 8.7 mg/dL), gouty tophi (21.6%, 21.0%), mean body weight (100.5 kg, 100.3 kg), median BMI (32.5 kg/m², 32.1 kg/m²), race: White (69.7%, 69.2%), Black (17.8%, 19.2%), American Indian or Alaska Native (8.5%, 7.5%), Native Hawaiian or other Pacific Islander (0.4%, 0.5%), Asian (3%, 3.1%), and other (0.6%, 0.5%).

[7] Cardiovascular death includes sudden cardiac death, acute myocardial infarction, heart failure death, stroke death, or other cardiovascular causes of death (arrhythmia, pulmonary embolism, etc.). Sudden Cardiac Death: refers to death that occurs unexpectedly in a previously stable patient and includes the following deaths: 1.Witnessed and instantaneous without new or worsening symptoms. 2. Witnessed within 60 minutes of the onset of new or worsening cardiac symptoms. 3. Witnessed and attributed to an identified arrhythmia (e.g., captured on an electrocardiographic (ECG) recording or witnessed on a monitor by either a medic or paramedic). 4. Subjects unsuccessfully resuscitated from cardiac arrest or successfully resuscitated from cardiac arrest but who die within 24 hours without identification of a non-cardiac etiology. 5. Unwitnessed death or other causes of death (information regarding the patient's clinical status within the week preceding death should be provided).

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Table 1 Results of primary endpoint, secondary endpoints (safety), all-cause death (Modified-ITT analysis)

	Febuxostat group[a] (3 098 patients)	Allopurinol group[a] (3 092 patients)	Hazard ratio [95% CI]	P value[c]
Primary endpoint	335 (10.8)	321 (10.4)	1.03 [0.87-1.23][b]	0.66 (0.002)
Secondary endpoints				
Cardiovascular death	134 (4.3)	100 (3.2)	1.34 [1.03-1.73]	0.03
Nonfatal myocardial infarction	111 (3.6)	118 (3.8)	0.93 [0.72-1.21]	0.61
Nonfatal cerebral stroke	71 (2.3)	70 (2.3)	1.01 [0.73-1.41]	0.94
Urgent revascularization for unstable angina	49 (1.6)	56 (1.8)	0.86 [0.59-1.26]	0.44
Composite endpoint composed of 3 factors: cardiovascular deaths, nonfatal myocardial infarction and nonfatal cerebral stroke	296 (9.6)	271 (8.8)	1.09 [0.92-1.28]	0.33
All-cause death	243 (7.8)	199 (6.4)	1.22 [1.01-1.47]	0.04

a) Number of patients who developed adverse events [percentage of patients who developed adverse events (%)]

b) 97%CI

c) The P value in parentheses is a one-sided P value of a test for a null hypothesis assuming that the hazard ratio with the objective of showing non-inferiority is 1.3 or greater. All other P values are to show the superiority of the febuxostat group to the allopurinol group and are calculated by Cox regression analysis.

3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013 Japan
E-mail: safety.info@pmda.go.jp

The breakdown of deaths was as shown in Table 2.

Table 2 Incidence of deaths in the CARES study

	Febuxostat group (3 098 patients)	Allopurinol group (3 092 patients)
Cardiovascular death	134 (4.3)	100 (3.2)
Sudden cardiac death	83 (2.7)	56 (1.8)
Cardiac failure	20 (0.6)	13 (0.4)
Cerebral stroke	8 (0.3)	11 (0.4)
Myocardial infarction	11 (0.4)	6 (0.2)
Arrhythmia	7 (0.2)	9 (0.3)
Valvular disease	3 (<0.1)	2 (<0.1)
Cardiac failure and respiratory failure	1 (<0.1)	1 (<0.1)
Cardiovascular haemorrhage	0	1 (<0.1)
Peripheral arterial disease	0	1 (<0.1)
Other	1 (<0.1)	0
Noncardiovascular death	109 (3.5)	99 (3.2)

Number of patients who developed adverse events [percentage of patients who developed adverse events (%)]

2.Report on CV risks and risk of death by febuxostat

2.1 Published literature

4 literatures were extracted [8] as the clinical studies / epidemiological studies to assess CV risks and risks of death of febuxostat (one of them is a report on the CARES study). Additionally, 4 literatures were extracted [9] as the meta-analyses to assess CV risks and risks of death of febuxostat. The overviews of a total of 7 literatures (Literatures 1 to 7) other than the literature reporting the CARES study are as follows. Although the meta-analysis incorporating the

[8] The literatures extracted in the following (1) to (3) were included. (1) Literatures applicable to the query for literature search described in the FDA Briefing Document at the FDA Advisory Board (literatures applicable to the 5 following queries by PubMed and Embase: 1. "Febuxostat" AND "Cardiovascular disease," 2. "Febuxostat" AND "CVD," 3. "Febuxostat" AND "allopurinol" AND "cardiovascular disease," 4. "Febuxostat" AND "Mortality," and 5. "Febuxostat" AND "allopurinol" AND "Mortality"), and the literatures extracted by using the inclusion criteria (selected literatures including the following information; study population: adults aged 18 years and older, exposure group: Febuxostat, control group: Allopurinol, outcome: cardiovascular events and death or all-cause death, study method: cohort study, case-control study, observational study including cross-sectional study), (2) literature extraction conditions extracted in literature search of the Briefing Report of the MAH at the FDA Advisory Board (search conditions unknown), and (3) literatures extracted by PMDA by using the same queries and inclusion criteria as the FDA in PubMed (period: October 15, 2018-May 22, 2019) (date of search: May 22, 2019).

[9] Literatures which investigated CV risks or an inhibitory effect of cardiovascular events of the treatment drugs for hyperuricemia including Febuxostat among “febuxostat AND meta-analysis” in PubMed by the MAH.

3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013 Japan
E-mail: safety.info@pmda.go.jp

CARES study (Literature 7) reports a higher incidence of CV death in the febuxostat group compared to the control groups (placebo group or allopurinol group), 6 other literatures (Literatures 1 to 6) do not report a presence of CV risks or risks of death in the febuxostat group compared to the control group.

(Literature 1) Febuxostat for Cerebral and CaRdiorenovascular Events PrEvEntion StuDy. Eur Heart J. 2019;40: 1778-86)

An open-label randomized study that aimed to compare the onset of cerebrovascular, CV and renal events in patients with hyperuricemia with or without administration of febuxostat was conducted in 141 medical institutions in Japan.

In this study, patients with hyperuricemia (serum urate concentration: ≥ 7.0 mg/dL, < 9.0 mg/dL) with one or more cerebrovascular, CV, and renal risks [(1) hypertension, (2) complicated by type 2 diabetes mellitus or renal disease, (3) a history of cerebral disease or CVD] aged 65 years and older were investigated. Guidance for improving lifestyle was provided to patients in both the febuxostat group and non-febuxostat group. Febuxostat was started from 10 mg/day, and the dosage was increased to 20 mg/day at Week 4 and thereafter, and to 40 mg/day at Week 8 and thereafter in the febuxostat group. In the non-febuxostat group, administration of allopurinol 100 mg/day was taken into consideration when serum urate concentration became higher than the level at enrollment. The follow-up period was set at 36 months. All 1 070 randomized patients (febuxostat group: 537 patients and non-febuxostat group: 533 patients) were included in the analysis set. Serum urate concentration (mean±SD) at the end of the follow-up period was 4.50±1.52 mg/dL in the febuxostat group and 6.76±1.45 mg/dL in the non-febuxostat group. Regarding the primary endpoint (composite endpoint composed of all-cause death, cerebrovascular disease, nonfatal coronary artery disease, cardiac failure requiring hospitalization, arteriosclerotic disease requiring treatment, renal disorder, and atrial fibrillation), HR of the febuxostat group versus the non-febuxostat group was 0.750 [95%CI: 0.592-0.950].

(Literature 2) Assessment of Cardiovascular Risk in Older Patients With Gout Initiating Febuxostat Versus Allopurinol. (Circulation. 2018; 138: 1116-26)

A population-based cohort study using the US Medicare claims data (2008-2013) was conducted in order to assess CV risks when allopurinol or febuxostat is administered to patients with gout. Propensity score matching of 1:3 was

conducted, and 24 936 patients in the febuxostat group and 74 808 patients in the allopurinol group were included. In both groups, 12% of the patients had CVD at baseline. The median duration of follow-up was 1.1 years in patients in the febuxostat group and 1.2 years in patients in the allopurinol group. The incidence of the primary endpoint, hospitalization due to myocardial infarction or cerebral stroke (per 100 person-years), was 3.43 [95%CI: 3.22-3.66] in the febuxostat group and 3.36 [95%CI: 3.25-3.49] in the allopurinol group, and the HR of the patients in the febuxostat group versus the patients in the allopurinol group was 1.01 [95%CI: 0.94-1.08]. With regard to the secondary endpoint, recurrent cardiac failure, the HR of the patients in the febuxostat group versus the patients in the allopurinol group was 0.94 [95%CI: 0.91-0.99]. For the secondary endpoints including myocardial infarction, cerebral stroke, coronary revascularization, novel cardiac failure, and death other than recurrent cardiac failure, the HR of the patients in the febuxostat group versus the patients in the allopurinol group was 1.03 [95%CI: 0.94-1.13], 0.98 [95%CI: 0.87-1.10], 0.95 [95%CI: 0.87-1.03], 1.05 [95%CI: 0.98-1.12], and 0.95 [95%CI: 0.89-1.02], respectively. The HR of all-cause death in the long-term use (>3 years) of the patients in the febuxostat group versus the patients in the allopurinol group was 1.25 [95%CI: 0.56-2.80].

(Literature 3) Major Cardiovascular Events in Patients with Gout and Associated Cardiovascular Disease or Heart Failure and Chronic Kidney Disease Initiating a Xanthine Oxidase Inhibitor. (Am Health Drug Benefits. 2017; 10: 393-401)

A retrospective cohort study by using US insurance claims databases (2009-2013) was conducted to evaluate the effect of febuxostat or allopurinol administration on major CV events in gout patients with CVD or cardiac failure, and gout patients with grade 3 or 4 chronic kidney disease. A total of 2 426 patients including 370 patients who received febuxostat and 2 056 patients who received allopurinol were evaluated. The median duration of follow-up was 9 months in the patients in the febuxostat group and 9.2 months in the patients in the allopurinol group. The incidence of the major CV events (per 1 000 person-years) was 51.8 [95%CI: 28-87] in patients who received febuxostat and 99.3 [95%CI: 84-117] in patients who received allopurinol, and the HR of the patients who received febuxostat versus the patients who received allopurinol was 0.52 [95% CI: 0.30-0.91].

(Literature 4) Hypersensitivity and Cardiovascular Risks Related to Allopurinol and Febuxostat Therapy in Asians: A Population-Based Cohort Study and Meta-Analysis. (Clin Pharmacol Ther. 2019; Jan 28. doi: 10.1002/cpt.1377. 1-11)

A cohort study was conducted to compare the risk of hypersensitivity of allopurinol and hypersensitivity and CV risks of febuxostat by using electronic medical records of the Chang Gung Memorial Hospital Health System (2012-2016), which covers approximately one-tenths of healthcare service in Taiwan. Furthermore, a meta-analysis incorporating 2 recent studies (CARES study and Literature 2) was conducted. Of 61 539 patients receiving the drugs (10 034 patients receiving febuxostat, 51 505 patients receiving allopurinol), the number of patients newly receiving the drugs was 17 687 (5 680 patients newly receiving febuxostat, 12 007 patients newly receiving allopurinol). Hypersensitivity was observed in 33 cases in patients newly receiving allopurinol (including 18 cases of severe skin adverse reactions) and 1 case in patients newly receiving febuxostat (without severe skin adverse reactions). The overall incidence of hypersensitivity (per 1 000 person-years) was 0.2 in patients newly receiving febuxostat and 2.7 in patients newly receiving allopurinol, which was lower in patients newly receiving febuxostat. Compared to patients newly receiving allopurinol, the HR of CVD (myocardial infarction, urgent revascularization for unstable angina, or cerebral stroke) was 1.16 [95%CI: 0.95-1.41] and the HR of CV death was 1.49 [95%CI: 0.47-4.70] in patients newly receiving febuxostat versus patients newly receiving allopurinol.

(Literature 5) Cardiovascular effects of urate-lowering therapies in patients with chronic gout: a systematic review and meta-analysis. (Rheumatology (Oxford). 2017; 56: 1144-53)

A systematic review of randomized clinical trials (RCT) of urate-lowering treatment (ULT) in gout was conducted to investigate the effect of ULT on urate-lowering treatment outcome in gout. A total of 3 084 references were collected, and the febuxostat group (n=3 631) and the allopurinol group (n=1 154) were derived from 4 studies after excluding references due to overlapping, absence of CV event reports, and non-RCT study design. Overall, a pooled analysis did not reveal a significant difference between the febuxostat groups and the allopurinol groups [febuxostat group versus allopurinol group: relative risk (RR) 1.69 [95% CI:0.54-5.34], P=0.37: Cochrane Q test]. CV events did not decrease over time, and there was no difference between studies with < 52 weeks, and those with 52

weeks or longer observation.

(Literature 6) Xanthine oxidase inhibitors for prevention of cardiovascular events: a systematic review and meta-analysis of randomized controlled trials. (BMC Cardiovasc Disord. 2018; 18: 1-11)

In a RCT compared to placebo or untreated cases, the mortality and the incidence of major adverse CV events MACE (CV death, nonfatal myocardial infarction, nonfatal cerebral stroke, and urgent revascularization for angina unstable), death, and total CV events by December 30, 2016 was investigated by using PubMed, EMBASE, Web of Science, Cochrane Central, and Lilacs databases in order to study the effect of xanthine oxidase inhibitors (XOI) on CV events.

As a result, the OR_p[10]of MACE was 0.71 [95%CI: 0.46-1.09] and the OR_p of death was 0.89 [95%CI: 0.59-1.33] in 81 articles (10,684 patients) analyzed for MACE with XOI. In the meantime, the OR_p of total CV events was 0.60 [95%CI: 0.44-0.82] and the OR_p of hypertension was 0.54 [95%CI: 0.37-0.80] with XOI. Furthermore, the OR_p of MACE was 0.42 [95%CI: 0.23-0.76] with XOI in patients with a history of ischemic event. XOI had no particular effect on the onset of CV events.

(Literature 7) Febuxostat and Cardiovascular Events: A Systematic Review and Meta-Analysis. (Int J Rheumatol. 2019; Article ID 1076189. 1-10)

In order to compare the febuxostat group and control groups and investigate MACE risks, studies published by March 2018 were searched by using MEDLINE and EMBASE databases. RCTs comparing febuxostat and placebo or control groups including allopurinol were included. The pooled relative risks (RR) of MACE (nonfatal myocardial infarction, angina, cardiac failure, ischemic coronary artery disease) and CV death were calculated. As a result, 374 studies were obtained, and 10 meta-analyses were reviewed among 25 RCTs included in the systematic review. Of 14 402 patients (median age: 54 years, 90% of them was males) included in the 10 meta-analyses, febuxostat was administered to 8 602 patients, allopurinol was administered to 5 118 patients, and placebo was administered to 643 patients. As a result of a pooled analysis, the RR of MACE was 0.9 [95% CI: 0.6-1.5] (P = 0.96: Cochran Q chi-squared test) with febuxostat compared to the control groups (placebo or allopurinol). The RR of CV-related

[10] Considering the expected scarcity of the events, this was analyzed by means of Peto OR.

death was 1.29 [95%CI: 1.01-1.66] (P=0.03: Cochran Q chi-squared test) with febuxostat. The RR of CV death with febuxostat was 0.73 [95% CI: 0.24-2.25] (P=0.64: Cochran Q chi-squared test) if the CARES study was excluded.

2.2 Special drug use-results survey

Between April 2012 and June 2018, 3 245 patients were collected as the safety analysis set, and the number of cerebrovascular and CV deaths was 35 cases in this survey (including 11 cases of unexplained death), which was comparable to the number of onset calculated from the expectation[11] at the start of the survey.

In addition, the onset of CV events and deaths of patients with similar background[12] to the patients enrolled in the CARES study was investigated. In this survey, the number of gout patients included in the population with similar background to the patients enrolled in the CARES study was 71, and the incidence of CV events, CV death, and all-cause death was 11.3% (8/71 patients), 1.4% (1/71 patients), and 4.2% (3/71 patients), respectively.

The number of patients in the population including patients with hyperuricemia was 723, and the incidence of CV events[13], CV death, and all-cause death was 9.5% (69/723 patients), 1.4% (10/723 patients), and 3.5% (25/723 patients), respectively.

2.3 Adverse reaction reports in Japan

Of 555 serious adverse reactions in 397 cases reported between the marketing approval of febuxostat and May 17, 2019, there were 70 CV related events[14] in 63 patients (including 18 cases of death outcome). In the evaluation by PMDA,

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11 In this survey, the number of deaths was expected based on the existing information prior to the start, and the onset of 20 to 30 cases of cerebral and cardiovascular deaths was expected when a survey on 3 000 patients with gout and/or hyperuricemia with a 1.5-year follow-up period was conducted. Since 3 245 patients were included in the safety analysis set and the mean follow-up period was 2.25 years in this survey, the number of onsets of cerebral and cardiovascular deaths based on the expectation at the start of the survey is calculated to be approximately 32 to 49 cases.

12 Refer to inclusion and exclusion criteria of the CARES study.

13 Extraction conditions when investigating cardiovascular events by Global PSUR. Although each case was investigated and determined whether it is applicable to MACE in the Cardiovascular Endpoints Committee in the CARES study, it was not possible in the special drug use-results survey. Therefore, the cases were tabulated based on the conditions used in Global PSUR.

14 Events considered particularly related to cardiovascular system (PT “cerebellar infarction,” “cerebral haemorrhage,” “cerebral infarction,” “thalamus haemorrhage,” “hypertension,” “labile blood pressure,” “shock haemorrhagic,” “peripheral arterial occlusive disease,” “chest discomfort,” “chest pain,” “death,” and “sudden cardiac death” among the events classified into SOC “cardiac disorders,” HLGT “cardiac and vascular investigations (excl enzyme tests)” in SOC “Investigations,” and events classified into SOC “vascular disorders,” “general disorders and administration site conditions,” and “nervous system disorder.”

there were no cases where causal relationship between febuxostat and the reported CV related events or febuxostat and death could not be ruled out.

3. Descriptions in guidelines

3.1 Clinical Guidelines for the Management of Hyperuricemia and Gout, 3rd edition (Japanese Society of Gout and Nucleic Acid Metabolism)

Treatment of hyperuricemia and gout and the clinical positioning of febuxostat in Japan are as follows.

Drug therapy is recommended on the basis of lifestyle guidance also concerning coexisting renal impairment and cardiovascular diseases for the treatment of hyperuricemia and gout. Although drug therapy for asymptomatic hyperuricemia without gouty arthritis is not recommended[15] in Europe and the United States, it is recommended to take drug therapy into consideration for asymptomatic hyperuricemia in order to prevent the onset of gouty arthritis at an early stage and to suppress the onset of cardiovascular diseases attributed to hyperuricemia and coexisting diseases (e.g., hyperlipidemia, hypertension, abnormal glucose tolerance) in Japan. It is recommended to take drug therapy into consideration with serum urate concentration of 8.0 mg/dL or greater when patients are complicated by renal impairment, urinary calculus, hypertension, ischemic heart disease, or diabetes mellitus, and the rough criteria to start drug therapy are set lower compared to 9.0 mg/dL without complication.

Treatment drugs for hyperuricemia in Japan are largely classified into uric acid synthesis inhibitors, uricosuric agents, or uricolytic enzymes, and febuxostat is categorized as a uric acid synthesis inhibitor along with allopurinol and topiroxostat. Although there is no priority in selecting uric acid synthesis inhibitors, they are used differently considering the presence of complications such as renal impairment and urinary calculus.

3.2 Guidelines for Diagnosis and Treatment of Acute and Chronic Heart Failure (2017 Revision) (Japanese Circulation Society)

Hyperuricemia is described as follows:

Hyperuricemia is a comorbidity often observed in patients with cardiac failure. The relationship between serum urate concentration and prognosis in patients with cardiac failure has been suggested, and the pathophysiological significance

[15] EU：2016 updated EULAR evidence-based recommendations for the management of gout.
US：2012 American College of Rheumatology guidelines for management of gout.

of uric acid in cardiac failure has attracted attention but the details are largely unknown. It has been reported that a serum urate concentration of 9.5 mg/dL or greater may be a marker for poor prognosis; however, no effective results regarding improvement of prognosis were obtained in an intervention study in patients with cardiac failure receiving allopurinol, although uric acid level was decreased. Research is underway at present on the effects of new uric acid inhibitors such as febuxostat and topiroxostat on cardiac failure. However, there is no conclusive evidence about whether or not hyperuricemia or its treatment drug affects the disease condition or prognosis at this point.

Many of the patients with cardiac failure are complicated by hypertension, ischemic heart disease, diabetes mellitus or chronic kidney disease as their underlying conditions. In Japan, it is considered desirable to take drug therapy into consideration following lifestyle guidance for hyperuricemia for patients with gouty arthritis / gouty tophus with a serum urate concentration greater than 7.0 mg/dL and patients with a serum urate concentration of 8.0 mg/dL or greater and complicated by renal impairment, hypertension, ischemic heart disease, or diabetes mellitus. Although there is no clear evidence indicating specific levels to which serum urate concentration should be controlled in patients with chronic cardiac failure, it is considered reasonable to aim to have the serum urate concentration at 7.0 mg/dL or below considering the above background.

3.3 JCS 2018 Guideline on Diagnosis of Chronic Coronary Heart Diseases (Japanese Circulation Society)

Hyperuricemia is described as follows.

There has been long years of debate on whether hyperuricemia is a risk factor of arteriosclerotic disease with no convincing conclusion reached. It is more likely that serum urate concentration is an independent risk factor of hypertension and coronary artery disease based on the recent meta-analyses. It is reasonable to provide appropriate urate-lowering treatment to control the onset of gout and renal impairment associated with hyperuricemia; however, the evidence of intervention studies is poor, and further study results should be awaited to decide whether the treatment leads to control cardiovascular events.

3.4 Japan Atherosclerosis Society (JAS) Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2017 (Japan Atherosclerosis Society)

Hyperuricemia has been added to the disease conditions that should be

considered as a risk factor of atherosclerotic diseases and is described as follows:

The clinical guidelines for the management of hyperuricemia and gout (2nd edition) state that the serum urate concentration: 1) can be an independent predictor of the risk index for the development of hypertension, 2) may be a potential predictor of risk of index and recurrent cerebral stroke, prognosis of cardiac failure, and re-hospitalization.

On the other hand, conflicting results have been reported on whether the serum urate concentration could be an independent risk factor of cardiovascular diseases.

In later reports including meta analyses, it was stated that urate concentrations can be an independent risk for hypertension or coronary artery events. Urate concentrations were also an independent risk of cerebral cardiovascular death in the EPOCH-JAPAN study[16], which analyzed 13 Japanese cohort studies.

By contrast, evidence supported in intervention studies is scarce on whether urate-lowering therapies can contribute to the reduction of atherosclerotic disease or improvement of its prognosis. Further work is needed to clarify the issue. Urate-lowering therapies with allopurinol, however, were effective in lowering blood pressure as observed in a meta-analysis of interventional studies, and a study that compared the allopurinol group and the propensity score-matched control group in elderly patients with hypertension also recognized the effectiveness of allopurinol to reduce the risk of cerebral stroke and coronary artery events (acute myocardial infarction, acute coronary syndrome). The effectiveness was particularly noted in higher doses.

IV. PMDA's determination based on the results of investigation

Based on the following reasons, PMDA considers that measures such as restricting the indication of febuxostat to inadequate responders to allopurinol or patients intolerant to the drug, thus changing the positioning of febuxostat, are not required at this point in Japan.

(1) Considering the CARES study results indicate relative risk ratio of febuxostat and allopurinol and some studies show that allopurinol reduces CV risks[17] or

[16] Relation of blood pressure and all-cause mortality in 180 000 Japanese participants: pooled analysis of 13 cohort studies.

[17] Hypertension. 2008; 51: 1483-91.

risk of death[18], it is not necessarily interpreted that febuxostat itself increases the risk of CV death. Moreover, it was planned not to adjust the multiplicity of the secondary endpoints and other safety endpoints; therefore, there may be the effect of the absence of multiplicity adjustment of the results of the hazard ratios of CV death and all-cause death. The following points were taken into consideration in interpretation of the CARES study results.

i. Effects of the ratio of patients who discontinued treatment on interpretation of the study results

In the CARES study, 57.3% of the randomized patients (1 777/3 101 patients) in the febuxostat group and 55.9% of the randomized patients (1 732/3 097 patients) in the allopurinol group discontinued[19] administration. Although more than 50% of the patients discontinued administration in each group, PMDA considers that it has only a small effect on the interpretation of the CARES study results since the ratio of the patients discontinued and the breakdown of the reasons for discontinuation are comparable in both groups.

ii. Effects of the ratio of patients who died after treatment discontinuation on interpretation of the study results

In the CARES study, all-cause death occurred in 85.2% (207/243 patients) in the febuxostat group and 86.4% (172/199 patients) in the allopurinol group, and CV death occurred in 82.8% (111/134 patients) in the febuxostat group and 86 % (86/100 patients) in the allopurinol group after discontinuation of the investigational drug [20].

Since the incidence after treatment discontinuation has the same tendency in both groups, PMDA considers that the ratio of the patients who died after treatment discontinuation has only a small effect on the interpretation of the study results.

(2) In light of the report that CV risk is lower in Japanese individuals compared to European and American individuals[21] and there was no difference in the incidence of CV events and CV death between febuxostat and allopurinol in a population-based cohort study in Asian gout patients, it is unknown whether the difference of the risk of cardiovascular death between allopurinol and febuxostat observed in the CARES study, with approximately 70% of the

[18] Weisman A, et al. Diabetes Obes Metab. 2019 Jun;21(6):1322-1329
[19] N Engl J Med. 2018 Mar 29;378(13):1200-10 Supplementary Appendix Figure S1.
[20] https://www.fda.gov/media/121245/download Table 27 (last confirmed June 12, 2019)
[21] Japanese journal of cardiovascular disease prevention.2018;53(1):1-8

subjects being white and 3% Asian, can be extrapolated directly to the Japanese population.

(3) There are several multiple population-based cohort studies reporting that there was no difference in CV risk or risk of death between allopurinol and febuxostat.

(4) In the CARES study, the ureate-lowering efficacy [22] of febuxostat was confirmed and the usefulness of febuxostat as a uric acid inhibitor was not denied.

Furthermore, in the special drug use-results survey conducted in Japan (which did not compare febuxostat with allopurinol), the number of cerebrovascular deaths and CV deaths observed did not exceed the number of deaths expected in advance and no information requiring new safety measures based on the post-marketing status was obtained.

However, when considering the results regarding the risks of CV death and all-cause death obtained in CARES study with a certain level of accuracy, PMDA considers that in the Japanese population the risks may also be different between allopurinol and febuxostat. And given CV death itself is a serious event and highly observed in the febuxostat group compared to the allopurinol group in the CARES study, the following (1) and (2) measures should be taken.

(1) The CARES study results should be included in the Other Precautions section in the package insert to inform healthcare professionals.

(2) In the CARES study, although non-inferiority of febuxostat to allopurinol was shown for the primary endpoint (composite endpoint composed of 4 factors: CV death, nonfatal myocardial infarction, nonfatal cerebral stroke, and urgent revascularization for angina unstable), differences were observed in CV death which was a secondary endpoint. A cautionary statement regarding the onset of CVD in administering febuxostat should be included in the Important Precautions section as a preventive measure.

V. Expert discussion

PMDA's determination in the above IV. was supported by the expert advisors. The following opinions were presented by the expert advisors.

[22] N Engl J Med. 2018 Mar 29;378(13):1200-10 Supplementary Appendix Table S4.2

1. Interpretation of the CARES study results

- Regarding interpretation of the study results, it is difficult to interpret based on a test, not based on a confirmatory analysis. However, there is no choice to interpret that the results were obtained under a certain precision from the perspective of the estimated precision of the obtained data. Thus, it is not appropriate to interpret the hazard ratios of all-cause death and CV death as false positive based on only the fact that multiplicity adjustment was not considered. They should be interpreted as a certain signal. A report that there is no difference in risk of death or CVD between the febuxostat group and the control groups has been mentioned, but it should be only natural that the CARES study results are not consistent with the trend of small-scale studies and studies with insufficient precision to capture the events.
- The CARES study was conducted in institutions in the United States, Canada, and Mexico, and approximately 70% of the subjects were white with only 3% Asian subjects; therefore, it is considered that the magnitude of the risk confirmed in the study results cannot be directly applied to Japanese patients.

2. Necessity of safety measures in Japan

2.1 No measures to be taken such as restricting febuxostat to patients who inadequately respond or are intolerant to allopurinol treatment

- It is considered that the CARES study results should be accepted as a signal with a certain significance and the possibility that CV death occurs frequently with febuxostat compared to allopurinol could not be denied. Although the difference in the risk of CV death of febuxostat is unknown, considering the result that there was no increase in risk of death or CV risk in patients taking febuxostat in the population-based observational study using propensity score matching in Taiwan, it is unlikely that the risks of febuxostat are high in Asians at least. Generally, the risk of CV events is lower in Japan compared to Europe and the US, thus it is considered that the CV risk level of febuxostat is not high enough to require restrictions on patients who are administered it.
- As all-cause death and CV death are serious events and they were reported in the CARES study, the study results should be notified to healthcare professionals and information collection (by post-marketing surveillance,

and so on) and evaluation in Japanese patients are considered necessary.

2.2 CARES study results and caution for CVD onset in administering febuxostat added to the package insert

- While simple extrapolation of CARES study results to Japanese patients could not be necessarily supported, it is considered appropriate to notify the results of CARES study as evidence identified overseas to healthcare professionals to be an aid as a basis of their selection of drugs.
- Significant differences were also reported in all-cause death in CARES study, and the differences should be noted when including CARES study results in the package insert.
- It would be better to include information on an increased risk of CV death, which is a serious adverse event, albeit reported in a foreign study.
- While including an alert for the onset of CVD in the package insert is considered appropriate, the description should note that caution should be exercised also for exacerbation of existing or for new onset of CVD since patients applicable to administration of febuxostat often have CVD already.
- CARES study actually showed significant differences in CV death as a secondary endpoint, not in CVD. Whereas, if an alert for the onset of CV death is included in the package insert, it would be difficult to implement any concrete measures to exercise caution for the onset of CV death in the clinical practice. Consequently, the alert has to be directed to the onset of CVD.
- Given the small size of Asian subjects in CARES study, it should be necessary to present the ethnic breakdown of subjects in the Other Precautions section.

VI. Overall evaluation

Based on the above survey, PMDA considers:

- It is appropriate to add the CARES study results concerning CV death to the package insert as shown in Appendix 2, noting the required caution for the onset of CVD.
- It is also appropriate to utilize relevant materials to provide information on the details of the study.
- The differences observed in all-cause death should be informed as well.
- It is considered necessary to continue the collection of information on CV

events in Japan through methods such as observational studies using databases.

Although no concerns were expressed about CV risks in a similar drug with a xanthine oxidase inhibitory effect, topiroxostat[23] at the time of its review, and the relation between the xanthine oxidase inhibitory effect and CV risk onset is unknown, it is considered appropriate to add the CARES study results to the package insert to inform healthcare professionals, in light of the event with a difference among similar drugs confirmed in the CARES study being a serious event, CV death.

[23] Topiroxostat was approved for marketing in June 2013. There is no overseas approval for marketing as of the end of May 2019.

(Appendix 1)

【Cardiovascular description in overseas package inserts】

USPI（Uloric USPI）（Updated February 2019）	European SmPC (ADENURIC SmPC) (Updated January 2019）
WARNING: CARDIOVASCULAR DEATH Gout patients with established cardiovascular (CV) disease treated with ULORIC had a higher rate of CV death compared to those treated with allopurinol in a CV outcomes study *[see Warnings and Precautions (5.1)]*. Consider the risks and benefits of ULORIC when deciding to prescribe or continue patients on ULORIC. ULORIC should only be used in patients who have an inadequate response to a maximally titrated dose of allopurinol, who are intolerant to allopurinol, or for whom treatment with allopurinol is not advisable *[see Indications and Usage (1)]*. 1. INDICATIONS AND USAGE ULORIC is a xanthine oxidase (XO) inhibitor indicated for the chronic management of hyperuricemia in adult patients with gout	

who have an inadequate response to a maximally titrated dose of allopurinol, who are intolerant to allopurinol, or for whom treatment with allopurinol is not advisable. For the safe and effective use of allopurinol, see allopurinol prescribing information. Limitations of Use: ULORIC is not recommended for the treatment of asymptomatic hyperuricemia. 5 WARNINGS AND PRECAUTIONS 5.1 Cardiovascular Death In a cardiovascular (CV) outcome study (ClinicalTrials.gov identifier NCT01101035), gout patients with established CV disease treated with ULORIC had a higher rate of CV death compared to those treated with allopurinol. The CV outcomes study in patients with gout (CARES) was a randomized, double-blinded, allopurinol-controlled, non-inferiority study conducted to evaluate the risk of major adverse cardiovascular events (MACE) in patients with gout who were treated with ULORIC. The study enrolled patients who had a history of major CV disease, cerebrovascular disease or diabetes mellitus with micro-and/or macrovascular disease. The	4.4 Special warnings and precautions for use *Cardio-vascular disorders* Treatment with febuxostat in patients with ischaemic heart disease or congestive heart failure is not recommended. A numerical greater incidence of investigator-reported cardiovascular APTC events (defined endpoints from the Anti-Platelet Trialists' Collaboration (APTC) including cardiovascular death, non-fatal myocardial infarction, non-fatal stroke) was observed in the febuxostat total group compared to the allopurinol group in the APEX and FACT studies (1.3 vs. 0.3 events per 100 Patient Years (PYs)), but not in the CONFIRMS study (see section 5.1 for detailed characteristics of the studies).

primary endpoint was the time to first occurrence of MACE defined as the composite of CV death, nonfatal MI, nonfatal stroke, or unstable angina with urgent coronary revascularization. The study was designed to exclude a prespecified risk margin of 1.3 for the hazard ratio of MACE. Results showed that ULORIC was non-inferior to allopurinol for the primary endpoint of MACE [Hazard Ratio: 1.03, 95% Confidence Interval (CI): 0.89, 1.21]. However, there was a significant increase in CV deaths in patients treated with ULORIC (134 [1.5 per 100 patient-years]) compared to patients treated with allopurinol (100 [1.1 per 100 patient-years]) [Hazard Ratio: 1.34, 95% CI: 1.03, 1.73]. Sudden cardiac death was the most common cause of adjudicated CV deaths in the ULORIC group (83 of 3,098; 2.7%) as compared to the allopurinol group (56 of 3,092; 1.8%). ULORIC was similar to allopurinol for nonfatal MI, nonfatal stroke and unstable angina with urgent coronary revascularization *[see Clinical Studies (14.2)].* Because of the increased risk of CV death, ULORIC should only be used in patients who have an inadequate response to a maximally titrated dose of allopurinol, who are intolerant to allopurinol, or for whom treatment with allopurinol is not advisable *[see Indications and Usage(1)]*.	The incidence of investigator-reported cardiovascular APTC events in the combined Phase 3 studies (APEX, FACT and CONFIRMS studies) was 0.7 vs. 0.6 events per 100 PYs. In the long-term extension studies the incidences of investigator-reported APTC events were 1.2 and 0.6 events per 100 PYs for febuxostat and allopurinol, respectively. No statistically significant differences were found, and no causal relationship with febuxostat was established. Identified risk factors among these patients were a medical history of atherosclerotic disease and/or myocardial infarction, or of congestive heart failure. .

Consider the risks and benefits of ULORIC when deciding to prescribe or continue patients on ULORIC *[see Indications and Usage (1)]*. Consider use of prophylactic low-dose aspirin therapy in patients with a history of CV disease. Physicians and patients should remain alert for the development of adverse CV event signs and symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur. 6 ADVERSE REACTIONS The following serious adverse reactions are described elsewhere in the prescribing information: ・Cardiovascular Death *[see Warnings and Precautions (5.1)]* 6.1 Clinical Trials Experience <u>Less Common Adverse Reactions</u> *Cardiac Disorders*: angina pectoris, atrial fibrillation/flutter, cardiac murmur, ECG abnormal, palpitations, sinus bradycardia, tachycardia.	4.8 Undesirable effects Cardiac disorders: <u>Uncommon</u> Atrial fibrillation, palpitations, ECG abnormal

[Proposed revisions] Febuxostat (branded name: Feburic Tablets 10 mg, 20 mg, 40 mg) (Appendix 2)

Underlines indicate alterations

Current	Proposed revision
2. Important Precautions (1)-(2) (snip) (N/A)	2. Important Precautions (1)-(2) (snip) (3) An overseas clinical study has shown that the incidence of cardiovascular death was higher in the febuxostat group than the allopurinol group in patients with gout who had cardiovascular disease. Caution is required for exacerbation or novel onset of cardiovascular diseases when febuxostat is administered (refer to the Other Precautions.).
9. Other Precautions (1)-(2) (snip) (N/A)	9. Other Precautions (1)-(2) (snip) (3) A double-blind, non-inferiority study was conducted overseas in patients with gout who had cardiovascular disease. Results showed that febuxostat was non-inferior to allopurinol for the primary endpoint (a composite endpoint composed of cardiovascular death, nonfatal myocardial infarction, nonfatal cerebral stroke, and urgent revascularization for unstable angina). However, of the secondary endpoints, the incidence of cardiovascular death was 4.3% (134/3 098 patients) in the febuxostat group, higher than 3.2% (100/3 092 patients) in the allopurinol group (hazard ratio [95%CI]: 1.34 [1.03, 1.73]). Among cardiovascular deaths, sudden cardiac death was most commonly observed in both groups (febuxostat group: 2.7% (83/3 098 patients), allopurinol group 1.8% (56/3 092 patients).) The incidence of all-cause death in the febuxostat group and in the allopurinol group was 7.8% (243/3 098 patients) and 6.4% (199/3 092 patients), respectively, higher in the febuxostat group (HR was 1.22 [95%CI: 1.01-1.47].)

N/A: Not Applicable, because the section is not included in the current package insert.