Review Report

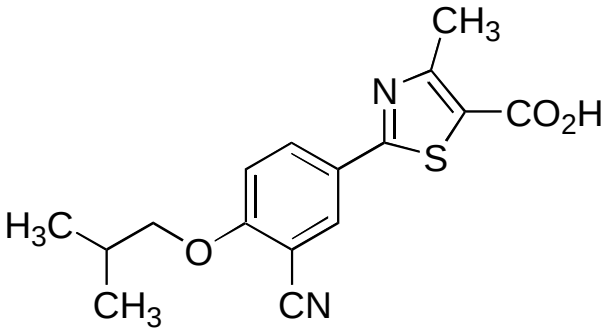
November 8, 2010

Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

Brand Name	Feburic Tablets 10 mg Feburic Tablets 20 mg Feburic Tablets 40 mg
Non-proprietary Name	Febuxostat (JAN*)
Applicant	Teijin Pharma Limited
Date of Application	December 25, 2009
Dosage Form/Strength	Tablets: Each tablet contains 10, 20, or 40 mg of Febuxostat.
Application Classification	Prescription drug (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{16}H_{16}N_2O_3S$
Molecular weight: 316.37
Chemical name:
2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid

Items Warranting Special Mention None

Reviewing Office Office of New Drug I

**Japanese Accepted Name (modified INN)*

Review Results

November 8, 2010

Brand Name	Feburic Tablets 10 mg Feburic Tablets 20 mg Feburic Tablets 40 mg
Non-proprietary Name	Febuxostat
Applicant	Teijin Pharma Limited
Date of Application	December 25, 2009

Results of Review

Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the efficacy of the product in the treatment of patients with gout or hyperuricemia has been demonstrated and its safety is acceptable in view of its observed benefits. The occurrence of gouty arthritis, adverse events related to thyroid function, liver function, or the cardiovascular system following treatment with febuxostat, and safety in patients with renal or hepatic impairment, elderly patients, and women, etc., need to be further investigated via post-marketing surveillance.

As a result of its regulatory review, PMDA has concluded that the product may be approved for the following indications and dosage and administration.

Indications	Gout and hyperuricemia
Dosage and Administration	The usual initial adult dosage is 10 mg of febuxostat administered orally once daily. The dose should be gradually increased as necessary, while monitoring blood urate levels. The usual maintenance dose should be 40 mg once daily. The dose may be adjusted according to the patient's condition. The maximum dose should be 60 mg once daily.

Review Report (1)

September 30, 2010

I. Product Submitted for Registration

Brand Name	Feburic Tablets 10 mg Feburic Tablets 20 mg Feburic Tablets 40 mg
Non-proprietary Name	Febuxostat
Applicant	Teijin Pharma Limited
Date of Application	December 25, 2009
Dosage Form/Strength	Tablets: Each tablet contains 10, 20, or 40 mg of Febuxostat.
Proposed Indication	Improvement of hyperuricemia in patients with the following diseases: Gout or hyperuricemia
Proposed Dosage and Administration	The usual adult dosage is 40 mg of febuxostat administered orally once daily. The dose may be adjusted according to the patient's condition. The maximum dose should be 60 mg once daily.

II. Summary of the Submitted Data and the Outline of the Review by Pharmaceuticals and Medical Devices Agency

The submitted data and the review thereof by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below.

1. Origin or history of discovery, use in foreign countries, and other information

Uric acid is mainly produced from hypoxanthine by liver xanthine oxidase (XOD) and excreted in urine by the kidneys. An enhanced formation of uric acid in the body or a decreased urate excretion in urine for any reason would lead to elevation of blood uric acid levels.

Patients with hyperuricemia, if left untreated for a long period, may suffer from gouty arthritis with severe pain, and if left further untreated, from frequent and protracted gouty arthritis, which could proceed to joint deformation/destruction due to formation of granulation tissue (gouty tophi) containing numerous urate crystals. These gouty arthritis and gouty tophi are often seen in the distal limb joints (especially in the first metatarsophalangeal joint), and cause a significant impairments in daily living such as difficulty in walking due to severe pain and reduced joint function. In addition, urate deposition in the kidneys may cause gouty kidney and then progress to uremia, which may be life-threatening.

At present, antihyperuricemic agents used in Japan include a uric acid production inhibitor (allopurinol) and uricosuric agents (benzbromarone, probenecid, and bucolome); allopurinol, the only uric acid production inhibitor, requires dose reduction in patients with renal impairment due to possible adverse drug reactions, while uricosuric agents have been reported to show reduced or no efficacy in patients with renal impairment.

Febuxostat, an XOD inhibitor discovered by Teijin Pharma Limited (formerly Teijin Limited), is the active ingredient of Feburic Tablets (hereinafter collectively referred to as Feburic). Feburic has been developed to be a novel uric acid production inhibitor that is expected to require no dose adjustment in patients with renal impairment.

A series of Japanese clinical studies of Feburic was initiated in 19[redacted] and a regulatory application was submitted in [redacted] 20[redacted]. However, the application was withdrawn in [redacted] 20[redacted] because further investigation was considered necessary to optimize the dosage regimen given the higher incidence of gouty arthritis in the febuxostat group than in the allopurinol group in the allopurinol-controlled double-blind comparative study (Study TMX-67-[redacted]). Subsequently, the applicant has submitted a regulatory application for Feburic with a claim that the efficacy and safety of Feburic administered in the newly

selected dose escalation protocol have been confirmed on the basis of the additional study results including a placebo-controlled dose-response comparative study (Study TMX-67-[redacted]).

Febuxostat was approved in Europe in April 2008, in the U.S. in February 2009, and in South Korea in June 2009.

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

Febuxostat, the drug substance, is manufactured at [redacted]. Its manufacturing process consists of [redacted] in Step [redacted], and [redacted] in Step [redacted]. [redacted] in Step [redacted], and [redacted] in Step [redacted]. Packaging, storage, and testing of the drug substance are performed in Step [redacted]. Step [redacted] has been defined as the critical step, and [redacted] have been defined as the control items. In addition, [redacted] (liquid chromatography [HPLC]), [redacted] (loss on drying), and [redacted] were controlled for appearance, identification (infrared spectrophotometry [IR] and HPLC), related substances ([redacted], [redacted] [HPLC]), and assay (HPLC) in Step [redacted]; and [redacted] (HPLC) and [redacted] are controlled for appearance, identification (IR and HPLC), related substances ([redacted], [redacted] [HPLC]), and assay (HPLC) in Step [redacted]. [redacted].

The drug substance is a white powder and its chemical structure has been elucidated by elemental analysis, mass spectrometry, ultraviolet spectrophotometry, IR, nuclear magnetic resonance spectroscopy, crystalline polymorphism (X-ray powder diffraction pattern, IR, [redacted], [redacted], [redacted], differential scanning calorimetry, thermogravimetry, dissolution rate, saturated solubility), and particle size. Physicochemical properties including description, solubility, hygroscopicity, melting point, thermal decomposition, pH, dissociation constant, and partition coefficient have been determined. The following 5 crystalline polymorphs are obtained by recrystallization of the drug substance using [redacted] in the manufacturing process: III ([redacted]), IV, I, V ([redacted]), and II ([redacted]).

The proposed specifications for the drug substance include description, identification (IR), heavy metals, related substances ([redacted], [redacted] [HPLC[1]]), residual solvents ([redacted]), loss on drying, residue on ignition, X-ray powder diffraction, [redacted], and assay (HPLC). In addition, although not included in the proposed specifications, identification (HPLC), [redacted], microbial limits, and assay ([redacted]) have also been determined.

Long-term (25°C/60% RH, [redacted] months) and accelerated (40°C/75% RH, 6 months) studies have been conducted on 3 batches ([redacted]) of the drug substance stored in a [redacted] ([redacted], [redacted]) polyethylene bag placed in a [redacted] drum. These studies evaluated attributes including description, identification (IR), related substances ([redacted], [redacted] [HPLC]), loss on drying, X-ray powder diffraction, [redacted], and assay (HPLC). In addition, a long-term testing (30°C/65% RH, [redacted] months) on 3 batches ([redacted]) of the drug substance stored in the same packaging configuration as was used for [redacted] was conducted to evaluate attributes including description, related substances ([redacted], [redacted] [HPLC]), loss on drying, X-ray powder

[1] [redacted].

diffraction, [redacted], and assay (HPLC). Furthermore, stress testing (temperature [70°C, 3 months, polyethylene bag/[redacted] drum], temperature/humidity [50°C, 60°C and 70°C, 3 months, sealed brown glass bottle[2]], light [D65 fluorescent lamp, cumulative illumination of ≥1.2 million lux·hr, integrated near ultraviolet energy ≥200 W·h/m^2, open Petri dish]) was conducted on 1 batch ([redacted]) to evaluate attributes including description, related substances ([redacted], [redacted] [HPLC]), loss on drying, X-ray powder diffraction, and assay (HPLC). As a result, no change from initial value was observed in any of the attributes. Based on the above results, a [redacted] period of [redacted] years has been proposed for the drug substance when packaged in [redacted], and stored at room temperature.

2.A.(2) Drug product

The drug product is film-coated tablets, which contain the drug substance, diluent, binder, disintegrator, lubricant, coating agent, and plasticizer. The proposed drug product contains 10, 20, or 40 mg of the drug substance. The drug product is packaged in PTP (polypropylene films/aluminum foils) or polyethylene bottles.

The drug product is manufactured by Teijin Pharma Limited. The manufacturing process for the drug product consists of [redacted] (Step [redacted]), [redacted] (Step [redacted]), [redacted] (Step [redacted]), [redacted] (Step [redacted]), and packaging/labeling/storage/testing (Step [redacted]). Among these, Step [redacted] has been defined as the critical step, during which [redacted] and hardness are controlled. In addition, intermediate product testing performed during Step [redacted] include description, identification (HPLC, ultraviolet-visible spectrophotometry), purity (HPLC), dissolution, uniformity of dosage units, and assay (HPLC). These control values and test methods are identical to specifications for the drug product.

During the pharmaceutical development, [redacted] was identified as the critical quality attribute because it largely affected on the dissolution and content uniformity, and defined as [redacted] based on a risk analysis.

The proposed specifications for the drug product include description, identification (HPLC, ultraviolet-visible spectrophotometry), purity (HPLC), dissolution, uniformity of dosage units, and assay (HPLC). In addition, although not included in the proposed specifications, purity (related substances), hardness, water content, microbial limits, [redacted], and X-ray powder diffraction have been determined. The intermediate product tests performed during Step [redacted] (description, identification, purity, dissolution, uniformity of dosage units, and assay) will serve as specifications for the final product.

Long-term (25°C/60% RH, [redacted] months for 10 and 20 mg tablets [[redacted] polyethylene bottle package, [redacted] months], [redacted] months for 40 mg tablets) and accelerated (40°C/75% RH, 6 months) studies have been conducted on 3 batches each of the drug product stored in a PTP package or polyethylene bottle package ([redacted]) ([redacted]). These studies evaluated attributes including description (appearance, odor), identification (HPLC, ultraviolet-visible spectrophotometry), dissolution, related substances ([redacted], [redacted] [HPLC]), hardness, water content, microbial limits, [redacted], and assay (HPLC). In addition, stress testing (temperature [60°C and [redacted]°C, 3 months, sealed glass bottle], humidity [25°C/75% RH, 3 months, open glass bottle], light [D65 fluorescent lamp, cumulative illumination of ≥1.2 million lux·hr, integrated near ultraviolet energy of ≥200 W·h/m^2, open Petri dish, PTP, [redacted], polyethylene bottle ([redacted])] was conducted on 1 batch ([redacted]) to evaluate attributes including description (appearance, odor), related substances ([redacted], [redacted] [HPLC]), dissolution, and assay (HPLC). Stress testing (temperature) and stress testing (humidity) evaluated also identification (HPLC, ultraviolet-visible spectrophotometry), hardness, and water content. As a result, [redacted] and [redacted] were observed in the long-term and accelerated studies. In the stress testing (temperature), changes in description (sweet and burnt odor; [redacted] for products stored at [redacted]°C only), [redacted], and [redacted] were observed, and products stored at [redacted]°C showed [redacted] and a slight increase in the content of impurities. In the stress testing (humidity), an increase in the water content and a decrease in the hardness were observed. In the stress testing (light), changes in description

[2] Sample was stored in open brown glass bottle at 40°C/75% RH for 1 week before sealing, and then the testing was started.

([redacted]), Related Substance A, and Degradation Products B, C, and D were observed for products stored in a Petri dish. Related Substance A, and Degradation Products B, C, and D were observed also for products stored in a PTP package. No change was observed in the other attributes.

Consequently, shelf lives of 3 years (10 and 20 mg tablets) and 2 years (40 mg tablets) have been proposed for the drug product when stored at room temperature in a PTP or a polyethylene bottle package.

2.B Outline of the review by PMDA

2.B.(1) Crystalline polymorphism

PMDA asked the applicant to explain the cause and prevention of ([redacted]) against the [redacted].

The applicant's response:
[redacted] because [redacted] was manufactured during the early phase of development when accumulated information on [redacted] was inadequate. Subsequent investigation on [redacted] revealed a possibility that [redacted]. Based on the above findings, [redacted]. [redacted] and [redacted] are controlled as the key parameters in the critical step.

Given the applicant's explanation that [redacted], PMDA asked the applicant to explain whether [redacted] needs to be controlled.

The applicant responded that [redacted] is controlled because [redacted].

PMDA accepted the applicant's response.

2.B.(2) Stability of intermediate product

Given the intermediate product testing performed during Step [redacted] was proposed as the testing and specifications for the final product, PMDA asked the applicant to explain the stability of the intermediate product.

The applicant's response:
The drug product may be stored in the form of the intermediate product until [redacted]. During this period of time, the products will be stored in [redacted]. For [redacted], the stability studies showed that the drug product stored in the proposed commercial package is stable for [redacted] months (10 and 20 mg tablets) or [redacted] months (40 mg tablets, study is ongoing) under the long-term storage condition, and for 6 months (all strengths) under the accelerated storage condition. Therefore, [redacted], storage in the form of the intermediate product does not affect the quality of the final product.

PMDA asked the applicant to provide the details of storage condition of the intermediate product (e.g., material and size of container, number of tablets) and to explain the appropriateness of assuming the stability of the intermediate product stored in that condition as well as the expected storage duration of the intermediate product, based on the stability data of the drug product stored in the proposed commercial package.

The applicant's response:
The intermediate product will be stored in [redacted] ([redacted] L). This package is [redacted] as is the case with the proposed commercial packages (PTP and polyethylene bottle), and thus it is appropriate to assume the stability of the intermediate product stored in that condition, based on the stability data of the drug product stored in the proposed commercial package. Additional stability studies with a [redacted] year storage period will be conducted in [redacted] on the intermediate product manufactured for process validation.

Since the long-term and accelerated stability data of the drug product stored in the proposed commercial package showed no substantial impact on the quality, PMDA has concluded that storage of the intermediate product is unlikely to significantly affect the specifications, and therefore, accepted the applicant's response.

Consequently, PMDA has concluded that the specifications and storage conditions proposed for the drug substance and the drug product, as well as [redacted] of the drug substance and shelf life of the drug product are acceptable.

3. Non-clinical data

3.(i) Summary of pharmacology studies

3.(i).A Summary of the submitted data

Primary pharmacodynamic (PD) studies included *in vitro* studies on activity and type of XOD inhibition, inhibition of nucleic acid metabolizing enzymes other than XOD, and inhibition of XOD by oxidative metabolites of febuxostat; and *in vivo* studies on antihyperuricemic activity in hyperuricemic and normal rats. Because the guideline of "Safety Pharmacology Studies for Human Pharmaceuticals" (PMSB/ELD Notification No. 902, dated June 21, 2001) had not yet been enforced at the time of initiation of safety pharmacology studies, studies other than the following were conducted as non-GLP studies to evaluate the effects on central nervous, respiratory, cardiovascular, and gastrointestinal systems, and isolated smooth muscles, water-electrolyte metabolism, blood coagulation system, and platelet aggregation: a study of the effect on hERG channels in HEK293 cells, a study of the effect on action potential in dog Purkinje fibers, and a study of the effects on respiratory and cardiovascular systems in unanesthetized dogs. No secondary PD studies were conducted. PD interaction studies performed included studies on the effects on combination therapy of antihypertensive (nifedipine) and hypoglycemic (glibenclamide) drugs.

3.(i).A.(1) Primary PD

3.(i).A.(1).1) *In vitro* pharmacology

(a) Activity and type of XOD inhibition (4.2.1.1-1)

The effect of febuxostat on uric acid production from xanthine was evaluated in purified bovine milk XOD. The results showed that febuxostat inhibited XOD through a mixed inhibition mechanism based on the Lineweaver-Burk plot. The Ki values for oxidized and reduced forms of XOD were 0.6 and 3.1 nmol/L, respectively, indicating both forms of XOD were inhibited.

(b) Effect on other nucleic acid metabolizing enzymes (4.2.1.1-2 to 4.2.1.1-6)

The effects of febuxostat (1, 10, 100 μmol/L) on metabolizing enzymes other than XOD, which are involved in purine metabolism (which generates uric acid as the end product) or metabolism of pyrimidines (components of nucleic acid like purines) were evaluated. The results showed that febuxostat had no effect on the activities of guanine deaminase, purine nucleoside phosphorylase (PNP), orotate phosphoribosyltransferase (OPRT), or orotidylate decarboxylase (OMPDC). Febuxostat had no effect on the activity of hypoxanthine-guanine phosphoribosyltransferase (HGPRT) at up to 10 μmol/L, but decreased the activity of HGPRT by 14.5% ± 18.9% (mean ± standard deviation [SD]) as compared with the control group at 100 μmol/L.

3.(i).A.(1).2) *In vivo* pharmacology

(a) Antihyperuricemic activity in uricase inhibitor-treated rats (4.2.1.1-7)

Anthropoids, such as humans and chimpanzees, lack uricase and excrete uric acid as the end product of purine metabolism, but most mammals including rodents have uricase to metabolize uric acid to highly-water-soluble allantoin. Antihyperuricemic activities of febuxostat and allopurinol were compared in hyperuricemia model rats pretreated with an uricase inhibitor (potassium oxonate).

A single oral dose of febuxostat (1, 3, or 10 mg/kg), allopurinol (3, 10, or 30 mg/kg), or vehicle (0.5% methylcellulose solution [0.5% MC solution]) was administered to male rats (n = 6/group) fed with diets containing 2.5% potassium oxonate, and $AUC_{0\text{-}6h}$ was calculated by linear trapezoidal rule from plasma urate levels at 0, 1, 2, and 6 hours post-dose. The results showed that both febuxostat and allopurinol

decreased plasma urate levels in a dose-dependent manner, leading to a significant decrease in the plasma urate $AUC_{0\text{-}6h}$ as compared with the vehicle control group at all dose levels studied. The rate of decrease in plasma urate levels ($AUC_{0\text{-}6h}$) relative to the vehicle control group was determined to be comparable between the febuxostat 1 mg/kg and allopurinol 3 mg/kg groups, between the febuxostat 3 mg/kg and allopurinol 10 mg/kg groups, and between the febuxostat 10 mg/kg and allopurinol 30 mg/kg groups.

(b) Effect on uric acid, allantoin, xanthine, and xanthine calculus formation in normal rats (4.2.1.1-8)

Male rats (n = 27-30/group) received orally febuxostat (1, 3, 10, 30, or 100 mg/kg), allopurinol (3, 10, 30, 100, or 200 mg/kg), or vehicle (0.5% MC solution) once daily (qd) for 28 days. Untreated male rats (n = 6) were also included in the evaluation. Blood was collected from 6 animals at 1, 2, 6, and 24 hours post-dose on Days 1 and 28. On Day 28, blood was collected at 0 and 24 hours post-dose from identical animals. Data from untreated rats were deemed as those at 0 hours on Day 1. Urine was collected from 0 to 6 hours post-dose and from 6 to 24 hours post-dose on Days 1 and 28, and from 0 to 24 hours post-dose on Days 3, 7, 14, and 21 from identical animals (n = 6/group). In addition, renal crystal deposition/calculi was histopathologically examined on the day after the last dose. The results showed decreases in urinary urate and total allantoin excretion and an increase in urinary xanthine excretion in the febuxostat and allopurinol groups as compared with the vehicle control group on Day 1, and even on Day 28. The dose-response curve for the decreases in urinary urate and total allantoin excretion on Day 1 and that for the increase in urinary xanthine excretion showed a similar pattern between the febuxostat and allopurinol groups, and febuxostat exhibited, at 1/30 to 1/10 times the dose of allopurinol, a comparable magnitude of effect obtained with allopurinol. In the febuxostat group, an increase in plasma xanthine levels and a decrease in plasma urate levels were observed, while allantoin levels remained high throughout the study. Based on the dose-response curve for the plasma xanthine AUC on Day 1, febuxostat exhibited, at 1/30 to 1/10 times the dose of allopurinol, a comparable magnitude of effect obtained with allopurinol, and when based on the plasma urate AUC, febuxostat exhibited a comparable magnitude of effect at 1/10 to 1/3 times the dose of allopurinol. Additionally, 1 of 30 animals in the febuxostat 10 mg/kg group and 2 of 30 animals in the allopurinol 30 mg/kg group showed xanthine crystal deposition and/or xanthine calculi in the kidney, and almost all animals in the febuxostat ≥30 mg/kg and allopurinol ≥100 mg/kg groups showed xanthine calculi; therefore, based on the incidence of xanthine calculus formation, febuxostat exhibited a comparable effect at approximately 1/3 times the dose of allopurinol.

(c) Plasma urate lowering activity in uricase inhibitor-treated rats with impaired renal function (4.2.1.1-9)

Male rats (n = 6/group) underwent 5/6 nephrectomy, and after 21 days, received a single oral dose of febuxostat (0.3, 1, or 3 mg/kg) or vehicle (0.5% MC solution) after an overnight fast. An uricase inhibitor (potassium oxonate) 62.5 mg/kg was subcutaneously administered at 1 hour before and 1, 3, and 5 hours after administration of febuxostat. $AUC_{0\text{-}6h}$ was calculated by linear trapezoidal rule from plasma urate levels at 0, 1, 2, and 6 hours post-dose. Additional rats that underwent sham operation (n = 6/group) received a single oral dose of febuxostat or vehicle in a similar manner. As a result, febuxostat decreased plasma urate levels ($AUC_{0\text{-}6h}$) in both the 5/6 nephrectomy and sham operation groups, and the inhibition rate relative to the vehicle control group and absolute decrease (difference in the plasma urate $AUC_{0\text{-}6h}$ between the vehicle control and febuxostat groups) were comparable between the 5/6 nephrectomy and sham operation groups.

3.(i).A.(1).3) Activity and mode of XOD inhibition by oxidative metabolites (4.2.1.1-1)

Inhibition of XOD by oxidative metabolites of febuxostat (67M-1[R],[3] 67M-1[S],[4] 67M-2, 67M-3, and 67M-4) was evaluated in purified bovine milk XOD. The results showed that all the metabolites inhibited XOD strongly, with the mode being a mixed inhibition like febuxostat. The Ki value for oxidized form of XOD was 0.6, 0.8, 1.6, 2.0, and 1.6 nmol/L, respectively, and the Ki value for reduced form of XOD was 3.7, 4.2, 4.4, 10.5, and 8.2 nmol/L, respectively.

[3] *R*-enantiomer of an oxidative metabolite (67M-1) of febuxostat
[4] *S*-enantiomer of an oxidative metabolite (67M-1) of febuxostat

3.(i).A.(2) Safety pharmacology

3.(i).A.(2).1) Effects on general symptoms (4.2.1.3-1)

A single oral dose of febuxostat (10, 30, 100, or 300 mg/kg) or vehicle (0.5% MC solution) was administered to male mice (n = 4/group), and general symptoms were examined by the Irwin test. As a result, decreased motor activity was observed in the 100 and 300 mg/kg groups.

3.(i).A.(2).2) Effects on central nervous system (4.2.1.3-2 to 4.2.1.3-6)

A single oral dose of febuxostat (10, 30, or 100 mg/kg) or vehicle (0.5% MC solution) was administered to male mice (n = 5/group), and the effects on locomotor activity were evaluated. The results showed a significant decrease in locomotor activity at 1 hour post-dose in the 30 mg/kg group, but no effect in the 100 mg/kg group. Additionally, effects on hexobarbital-induced sleep (n = 10/group), pentylenetetrazol- or electroshock-induced seizures (n = 10/group each), pain induced by acetic acid writhing test or hot plate test (n = 10/group each), and rectal temperature (n = 6/group) were evaluated. C_{max}[5] after a dose of febuxostat 30 mg/kg was 21.8 times the estimated C_{max} (6.2 μmol/L [2.0 μg/mL]) after a dose of febuxostat 60 mg/day, the proposed maximum dose.

3.(i).A.(2).3) Effect on respiratory and cardiovascular systems

(a) Effects on hERG channel current (4.2.1.3-7 and 4.2.1.3-8)

Effects of febuxostat (0, 0.1, 1, 50, and 500 μmol/L) were evaluated in HEK293 cells expressing hERG channels. The results showed that febuxostat did not inhibit hERG channel current during the repolarization phase but potentiated the current during the depolarization phase. No use- or temperature-dependency was observed. Then, hERG channel was introduced to CHO cells expressing no endogenous voltage-gated K^+ channels to evaluate voltage dependency of the hERG channel current potentiation by febuxostat (0, 0.0001, 0.001, 0.01, 0.1, 1, and 10 μmol/L). As a result, a voltage-dependent potentiation was observed, with particularly marked potentiation during the depolarization phase. A biphasic potentiation was seen during the depolarization phase, consisting of the peak response seen early (at 1-2 minutes) after treatment with febuxostat and a slightly weaker response seen at a steady state (at ≥3 minutes), and the EC_{50} values were 3 and 70 nmol/L, respectively. In addition, use-dependency of the hERG channel current potentiation by febuxostat (1 μmol/L) was evaluated; the potentiation was absent at 0.3 Hz while present at 3 Hz, indicating a use-dependency.

(b) Effects on action potential (4.2.1.3-9)

Effects of febuxostat (0, 0.1, 1, 50, and 500 μmol/L) were evaluated in Purkinje fibers isolated from canine myocardium. The results showed that, at a stimulus rate of 1 and 0.5 Hz, febuxostat 0.1 and 1 μmol/L did not affect the resting membrane potential (RMP), maximum rate of rise of depolarization (MRD), action potential amplitude (APA), or action potential durations at 60% and 90% repolarization (APD_{60} and APD_{90}, respectively). Febuxostat 50 μmol/L decreased the APA by 4 mV at a stimulus rate of 1 Hz and by 5 mV at a stimulus rate of 0.5 Hz, and decreased the MRD by 12% at a stimulus rate of 1 Hz and by 17% at a stimulus rate of 0.5 Hz, but these decreases were not significant as compared with the vehicle[6] control. On the other hand, febuxostat 50 μmol/L decreased APD_{60} and APD_{90} by 22% and 20%, respectively, at a stimulus rate of 1 Hz and by 26% and 25%, respectively, at a stimulus rate of 0.5 Hz; these decreases were significant as compared with the vehicle control. No effects were observed on the RMP. Febuxostat 500 μmol/L induced a depolarization of RMP at both stimulus rates. A total of 5 of 6 samples showed a loss of excitability with no action potential generation, and the remaining 1 sample showed substantial decreases in the APA and MRD at both stimulus rates. *dl*-Sotalol (50 μmol/L), the positive control, significantly increased APD_{60} and APD_{90} as compared with the vehicle control.

(c) Effects on Na^+ channel (4.2.1.3-10)

Effects of febuxostat (1, 10, 50, 100, and 500 μmol/L) were evaluated in HEK293 cells expressing human cardiac Na^+ channels. The results showed that, at a stimulus rate of 0.1 Hz, febuxostat suppressed the inward Na^+ current in a dose-dependent manner (IC_{50} value, 75 μmol/L). No such effects were

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[5] C_{max} in male animals in the 24 mg/kg group in the preliminary studies of mice carcinogenicity study (study Nos. 3500 [011-022] and 3501 [011-023], on Day 1)

[6] Physiological Salt Solution (PSS): 125 mM NaCl, 5.4 mM KCl, 1.8 mM $CaCl_2$, 1.0 mM $MgCl_2$, 1.2 mM NaH_2PO_4, 25 mM $NaHCO_3$, 5.5 mM D-glucose

observed at a stimulus rate of 0.3 or 3 Hz, indicating no use-dependency. Lidocaine (300 μmol/L), the positive control, suppressed the Na^+ current.

(d) Effects on Ca^{2+} channel (4.2.1.3-11)

Effects of febuxostat (5, 50, 100, and 500 μmol/L) were evaluated in guinea pig ventricular myocytes. The results showed that, at a stimulus rate of 0.05 Hz, febuxostat suppressed the Ca^{2+} channel current in a dose-dependent manner, but suppressed it only by 37% even at 500 μmol/L. No such effects were observed at a stimulus rate of 0.3 or 3 Hz, indicating no use-dependency. Nifedipine (0.1 μmol/L), the positive control, suppressed the Ca^{2+} current.

(e) Effects on respiratory rate, blood pressure, heart rate, left femoral artery blood flow, and electrocardiogram in anesthetized dogs (4.2.1.3-12)

Febuxostat (10 or 100 mg/kg) or vehicle (0.5% MC solution) was administered intraduodenally to anesthetized male dogs (n = 4/group), and respiratory rate, blood pressure, heart rate, left femoral artery blood flow, electrocardiogram, and left ventricular pressure were sequentially measured up to 240 minutes post-dose. As a result, no effects were observed. C_{max} (10.7331 μg/mL) after a dose of febuxostat 100 mg/kg was 5.4 times the estimated C_{max} (6.2 μmol/L [2.0 μg/mL]) after a dose of febuxostat 60 mg/day, the proposed maximum dose.

(f) Effects on respiratory rate, blood pressure, heart rate, and electrocardiogram in unanesthetized dogs (4.2.1.3-13)

Febuxostat (5 or 50 mg/kg) or vehicle (0.5% MC solution) was administered orally to unanesthetized dogs (n = 3/sex/group) for 14 days. As a result, febuxostat did not affect the respiratory rate or electrocardiogram, but caused an acutely decreased blood pressure persisting for 1.5 to 2 hours resulting in a 26% decrease in mean systolic pressure in 2 (1 male and 1 female) of 6 animals receiving 50 mg/kg on Day 1 and in 2 (1 male and 1 female) of 6 animals receiving 5 mg/kg on Days 6 to 7. Among the 4 animals with a decreased blood pressure, 1 animal in the 5 mg/kg group showed an insignificant decrease in heart rate with limited severity, which could be observed also during off-treatment period. The applicant discussed that each of these changes occurred just once in each affected animal during the repeated treatment at variable timing with variable duration in dose-independent manner, and therefore, are unlikely to be caused by febuxostat. C_{max} after a dose of febuxostat 50 mg/kg in male and female dogs (29.5607 and 46.7042 μg/mL, respectively) was 14.8 and 23.4 times, respectively, the estimated C_{max} (6.2 μmol/L [2.0 μg/mL]) after a dose of febuxostat 60 mg/day, the proposed maximum dose.

3.(i).A.(2).4) Effects on gastrointestinal system (4.2.1.3-14)

Male mice (n = 6/group) received a single oral dose of febuxostat (10, 30, or 100 mg/kg) or vehicle (0.5% MC solution). Febuxostat did not affect charcoal transit through the small intestine.

3.(i).A.(2).5) Effects on isolated ileal smooth muscles (4.2.1.3-15 and 4.2.1.3-16)

The effects of febuxostat (0, 3, 10, and 30 μmol/L) on contraction induced by different constrictors and spontaneous activity were evaluated in isolated ileum from male guinea pigs. The results showed no effects of febuxostat on contraction induced by acetylcholine, histamine, or barium chloride. The spontaneous activity was not affected by febuxostat at up to 10 μmol/L, but was slightly decreased by 30 μmol/L of febuxostat.

3.(i).A.(2).6) Effects on water-electrolyte metabolism (4.2.1.3-17)

Male rats (n = 6/group) received a single oral dose of febuxostat (10, 30, or 100 mg/kg) or vehicle (0.5% MC solution). As a result, increases in urine volume, urinary K excretion, and urinary Cl excretion were observed in the 100 mg/kg group. In addition, a significant increase in urinary xanthine excretion was observed in all dose groups as compared with the vehicle control group.

3.(i).A.(2).7) Effects on blood coagulation system and platelet aggregation (4.2.1.3-18)

Febuxostat (0, 3, 10, 30, and 100 μmol/L) had no effect on the coagulation time of human blood (activated partial thromboplastin time and prothrombin time) or adenosine diphosphate-induced platelet aggregation.

3.(i).A.(3) PD interaction studies (4.2.1.4-1 and 4.2.1.4-2)

Since patients with hyperuricemia frequently have comorbid cardiovascular diseases such as hypertension and diabetes mellitus, effects of febuxostat on the pharmacological activity of nifedipine (an antihypertensive drug) and glibenclamide (a hypoglycemic drug), which are drugs expected to be used concomitantly in clinical practice, were evaluated. The effect on the activity of nifedipine was evaluated by a single oral dose of febuxostat (1 or 10 mg/kg) or vehicle (0.5% MC solution) to spontaneously hypertensive male rats (n = 8/group) immediately followed by a single oral dose of nifedipine (5 mg/kg). As a result, no effects were observed in the febuxostat 1 mg/kg group, while in the febuxostat 10 mg/kg group, a slight decrease in the antihypertensive activity of nifedipine at 10 minutes post-dose and no effects from 30 minutes to 6 hours post-dose were observed. Nifedipine increased heart rate, while febuxostat had no effect at any dose. The effect on the activity of glibenclamide was evaluated by a single oral dose of febuxostat (1 or 10 mg/kg) or vehicle (0.5% MC solution) to male rats (n = 8/group) immediately followed by a single oral dose of glibenclamide (3 mg/kg). Blood glucose was measured from immediately after treatment until 24 hours post-treatment and no effects of febuxostat on the hypoglycemic activity of glibenclamide were observed.

3.(i).B Outline of the review by PMDA

3.(i).B.(1) Antihyperuricemic activity of febuxostat

PMDA asked the applicant to explain antihyperuricemic activity of febuxostat expected in animal species lacking uricase (like humans) based on the study results or literature data.

The applicant's response:

In a report comparing the serum urate lowering activity between febuxostat and allopurinol in 3 male chimpanzees that received 5 mg/kg of either of these drugs orally once daily for 3 days (Komoriya K, et al., *Eur J Pharmacol.* 1993;250:455-460), the serum urate levels at 24, 48, and 72 hours after the first dose were decreased by 28.1%, 41.6%, and 45.1%, respectively, by allopurinol, and by 55.9%, 69.6%, and 73.6%, respectively, by febuxostat, demonstrating that the serum urate lowering activity at the same dose level was higher with febuxostat. In addition, comparative serum urate lowering activity between the 2 drugs was also reflected in the 24-hour total urinary urate excretion, which was decreased by 78.6% and 96.5% by allopurinol and febuxostat, respectively, at 72 hours after the first dose. Furthermore, because urinary xanthine levels for both drugs were elevated after administration as compared with baseline levels, which were the detection limit or below, serum urate lowering activity of febuxostat is considered to be stronger than that of allopurinol, although definitive comparison cannot be made based on these data obtained at one dose level.

PMDA concluded that although definitive comparison between febuxostat and allopurinol cannot be made based on these data of one dose level obtained from a study of short-term treatment (3 days), antihyperuricemic activity of febuxostat has been demonstrated. PMDA accepted the applicant's response.

3.(i).B.(2) Effects of febuxostat on cardiovascular system

PMDA asked the applicant to discuss the effects on the cardiovascular system in humans because of the following findings: (i) a concentration-dependent hERG channel current potentiation during the depolarization phase was observed from low concentrations in the study evaluating the effects of febuxostat on hERG channel current [see "3.(i).A.(2).3).(a) Effects on hERG channel current (4.2.1.3-7 and 4.2.1.3-8)"] and (ii) short-QT syndrome has been reported to be associated with sudden cardiac death and ventricular arrhythmia (Brugada R, et al., *Circulation.* 2004;109:30-35).

The applicant's response:

Short-QT syndrome is a syndrome that was initially reported in 2000 as a hereditary disorder characterized by familial sudden death, short ventricular refractory period, and inducible ventricular fibrillation. Mutations in genes encoding myocardial potassium channels (KCNH2, KCNQ1, and KCNJ2) have been reported to be involved in its etiology (Brugada R, et al., *Circulation.* 2004;109:30-35, Bellocq C, et al., *Circulation.* 2004;109:2394-2397, Priori SG, et al., *Circ Res.* 2005;96:800-807). It has been determined that these genetic mutations increase potassium channel current involved in ventricular repolarization, leading to action potential duration shortening in ventricular myocardium *in vitro* and electrocardiographic QT-interval shortening *in vivo*. Action potential duration shortening, QT-

interval shortening, and ventricular fibrillation were reported to be caused by drugs that increase hERG channel current in 2008 (Lu HR, et al., *Br J Pharmacol*. 2008;154:1427-1438) and possible involvement of electrocardiographic QT-interval shortening due to hERG channel current potentiation in the proarrhythmic effect has been proposed. However, careful review of *in vivo* and clinical data in addition to *in vitro* data is important given the limited data on the relationship between the magnitude of drug-induced QT shortening and drug-associated proarrhythmic effects (ventricular tachycardia and ventricular fibrillation). Since the evaluation in HEK293 cells expressing hERG channels (4.2.1.3-7) demonstrated the presence of hERG channel current potentiation during the depolarization phase, an evaluation in CHO cells expressing hERG channels was conducted (4.2.1.3-8). As a result, a voltage-dependent potentiation of hERG channel current by febuxostat was demonstrated, especially during the depolarization phase. A biphasic potentiation was observed during the depolarization phase, consisting of the peak response seen at 1 to 2 minutes after treatment with febuxostat (EC_{50} = 3 nmol/L) and a slightly weaker response seen during the period of steady-state current (at ≥3 minutes after treatment) (EC_{50} = 70 nmol/L). The study in dog Purkinje fibers (4.2.1.3-9) demonstrated significant decreases in APD_{60} and APD_{90} as well as slight decreases in MRD and APA at 50 μmol/L of febuxostat. After treatment with 500 μmol/L, 5 of 6 samples showed a loss of excitability with no action potential generation, and the remaining 1 sample showed substantial decreases in MRD and APA. In addition, in studies evaluating the effects on Na^+ and Ca^{2+} channels (4.2.1.3-10 and 4.2.1.3-11), febuxostat suppressed both channels in a dose-dependent manner; the IC_{50} value against Na^+ channel was 75 μmol/L, and febuxostat suppressed Ca^{2+} channel by only approximately 37% even at a concentration of as high as 500 μmol/L. Taking account of the above results, the shortening of APD_{60} and APD_{90} seen at ≥50 μmol/L in the evaluation in dog Purkinje fibers is considered to be a change caused primarily by Na^+ channel suppression. Based on the human plasma protein binding of febuxostat (97.8%-99.0%) and the estimated C_{max} (6.2 μmol/L [2.0 μg/mL]) of febuxostat at the proposed maximum dose (60 mg/day), C_{max} of unbound febuxostat in plasma is estimated to be 0.062 to 0.136 μmol/L. Therefore, the EC_{50} values for the biphasic potentiation of hERG channel current (3 and 70 nmol/L) are equivalent to approximately 0.02 to 0.05 times and 0.5 to 1.1 times, respectively, the estimated unbound C_{max} at the maximum proposed dose. However, in the study evaluating the effects on action potential in dog Purkinje fibers, no effect was observed at up to 1 μmol/L, which is equivalent to approximately 7 to 16 times the estimated unbound C_{max} at the maximum proposed dose. At concentrations of 50 μmol/L (equivalent to approximately 360 to 800 times the estimated unbound C_{max} at the maximum proposed dose) or higher, an action potential duration shortening attributed to Na^+ channel suppression was observed. On the other hand, in the *in vivo* dog telemetry study of 14-day repeated oral administration of febuxostat (4.2.1.3-13), no effect was observed on electrocardiographic QT/QTc-intervals even at a dose of 50 mg/kg, which resulted in an exposure (C_{max} on Day 14, 38.1225 μg/mL) equivalent to approximately 19 times the estimated human exposure (C_{max}, 2.0 μg/mL) to febuxostat at a dose of 60 mg/day. On the basis of above findings, febuxostat is unlikely to affect the cardiovascular system in humans for the following reasons: (i) No effect was observed at up to 1 μmol/L in the study evaluating the effects on action potential of dog Purkinje fibers although an *in vitro* study showed a hERG channel current potentiation even at low concentrations; (ii) no effect on electrocardiogram including QT interval was observed in the *in vivo* 14-day repeated dose telemetry study in dogs although an action potential duration shortening attributed to Na^+ channel suppression was observed at concentrations of ≥50 μmol/L; and (iii) the study evaluating QTc prolongation by febuxostat conducted in the U.S. (5.3.4.1-1) showed no QT/QTcF shortening.

PMDA's view:
Given the observed hERG channel current potentiation at concentrations lower than the estimated unbound concentrations (0.062-0.136 μmol/L) at the maximum proposed dose (60 mg/day), cardiovascular effects of febuxostat should continue to be investigated. In light of the above, cardiovascular effects in humans will be additionally reviewed in the clinical section [see "4.(iii).B.(3).6) Cardiovascular adverse events"].

3.(ii) Summary of pharmacokinetic studies

3.(ii).A Summary of the submitted data

Pharmacokinetics (PK) of ^{14}C-febuxostat was evaluated in mice, rats, and dogs following intravenous or oral administration. In addition, repeat-dose PK was evaluated based on toxicokinetics observed in toxicity studies. Radioactivity in biomaterials was measured with a liquid scintillation counter (detection

limit, twice the simultaneously measured background levels) or autoradiography. Structure of metabolites was analyzed with high performance liquid chromatography/mass spectrometry (LC-MS) or high performance liquid chromatography/tandem mass spectrometry (LC-MS/MS). Primary study results are shown below.

3.(ii).A.(1) Absorption (4.2.2.2-1 to 4.2.2.2-3, 4.2.3.1-2, 4.2.3.2-2 to 4.2.3.2-4, 4.2.3.3.2-3, 4.2.3.4.1-1, 4.2.3.4.1-3, 4.2.3.4.1-4, and 4.2.3.5.2-3)

The PK parameters of total plasma radioactivity or unchanged febuxostat following a single intravenous or oral dose of ^{14}C-febuxostat in male and female mice, male rats, or male dogs are shown in Table 1. Following intravenous administration, the plasma clearances of total radioactivity and unchanged febuxostat were 143.5 and 211.4 mL/h/kg, respectively, in rats and 539.1 and 1158.8 mL/h/kg, respectively, in dogs, and the volumes of distribution[7] of total radioactivity and unchanged febuxostat were 1107.7 and 505.9 mL/kg, respectively, in rats and 9736.8 and 3274.3 mL/kg, respectively, in dogs. The absolute bioavailability calculated from the ratio of plasma AUC_{inf} of unchanged febuxostat following intravenous or oral administration at a dose of 1 mg/kg was 78.4% in rats and 48.0% in dogs.

Table 1. PK parameters of total radioactivity and unchanged febuxostat in plasma following a single dose

Species	Route of administration	Dose level (mg/kg)	Sex	No. of animals	Analyte	t_{max}	C_{max}	AUC_{obs}	AUC_{inf}	$t_{1/2}$
Mouse	Intravenous (i.v.)	1	♂	6[a)]	Total radioactivity	-	3850[b)]	3355	3372	3.2
			♀			-	5097[b)]	6039	6063	3.2
	Oral (p.o.)	3	♂			0.5	1670	5037	5051	2.9
			♀			2.0	2020	11,420	11,465	3.0
Rat	i.v.	1	♂	5	Total radioactivity	-	8202.9 ± 508.0[b)]	6910.3	6967.1	48.5
					Unchanged febuxostat	-	7611.2 ± 672.1[b)]	4253.1	4730.6	4.2
	p.o.	1			Total radioactivity	0.25	1971.8 ± 1096.5	5894.0	5945.1	42.1
					Unchanged febuxostat	0.25	1669.0 ± 915.1	3095.6	3707.4	3.4
		3			Total radioactivity	0.25	7306.3 ± 623.9	21,666.8	21,791.3	55.7
					Unchanged febuxostat	0.25	7012.9 ± 791.2	11,524.9	16,490.0	4.8
		10			Total radioactivity	0.25	23,654.1 ± 7942.2	67,463.4	67,616.0	18.0
					Unchanged febuxostat	0.25	21,219.0 ± 7202.3	38,276.2	45,920.8	3.0
Dog	i.v.	1	♂	3	Total radioactivity	-	2588.8 ± 190.3[c)]	1715.7±185.1	1855.7 ± 42.3	12.4 ± 5.1
					Unchanged febuxostat	-	2242.5 ± 231.7[c)]	869.4 ± 114.5	872.9 ± 113.9	2.0 ± 0.4
	p.o.	1			Total radioactivity	0.4 ± 0.1	387.0 ± 91.2	797.2 ± 155.3	838.8 ± 152.7	7.1 ± 1.5
					Unchanged febuxostat	0.4 ± 0.1	294.2 ± 73.6	370.1 ± 51.5	419.5 ± 55.6	18.1 ± 28.7

Mean ± SD (The mean of 2 pooled samples [3 animals/pool] for mice. Parameters other than C_{max} were calculated from the mean plasma concentrations for rats); -, Not calculated.

t_{max}, Time to reach the maximum concentration (in hours); C_{max}, Maximum concentration (in ng eq./mL [ng eq./g for mice] for total radioactivity and in ng/mL for unchanged febuxostat); AUC_{obs}, Area under the concentration-time curve to the last time point (in ng eq.·h/mL [ng eq.·h/g for mice] for total radioactivity and in ng·h/mL for unchanged febuxostat); AUC_{inf}, Area under the concentration-time curve extrapolated to infinity (in ng eq.·h/mL [ng eq.·h/g for mice] for total radioactivity and in ng·h/mL for unchanged febuxostat); $t_{1/2}$, Elimination phase half-life (in hours)

a) Number of animals at each blood sampling time point
b) Measured value at the initial time point (at 6 minutes post-dose for mice and 5 minutes post-dose for rats)
c) Time-zero value estimated by extrapolation from data up to 0.5 hours post-dose.

On Day 14 of 14-day treatment with oral doses of ^{14}C-febuxostat 1 mg/kg qd in male rats (n = 3-5), t_{max} was 0.25 and 0.25 hours for total plasma radioactivity and plasma unchanged febuxostat, respectively; C_{max} was 1016.2 ng eq./mL and 687.7 ng/mL, respectively; AUC_{obs} was 5445.0 ng eq.·h/mL and 2345.3 ng·h/mL, respectively; AUC_{inf} was 5653.0 ng eq.·h/mL and 3483.1 ng·h/mL, respectively; and the mean $t_{1/2}$ was 58.4 and 5.7 hours, respectively.

[7] Steady-state volume of distribution for rats and elimination phase volume of distribution for dogs

Toxicokinetic evaluation based on the toxicity study data showed that the mean ratio (female/male) of serum $AUC_{0\text{-}24h}$ of unchanged febuxostat was 3.3 to 3.9 in mice (3-48 mg/kg qd [13 weeks of administration]), 0.8 to 1.6 in rats (3-450 mg/kg [single dose], 3-150 mg/kg qd [13 weeks], and 3-48 mg/kg qd [26 weeks]), and 1.2 to 4.1 in dogs (5-80 mg/kg qd [13 weeks] and 5-45 mg/kg qd [52 weeks]), a more than dose-proportional increase in $AUC_{0\text{-}24h}$ was observed in male and female dogs. In pregnant rabbits (3-48 mg/kg/day [13 days]), $AUC_{0\text{-}24h}$ of unchanged febuxostat in serum was increased in a roughly dose-proportional manner.

3.(ii).A.(2) Distribution (4.2.2.2-3, 4.2.2.3-1, 4.2.2.3-6, and 4.2.2.3-7)

Following a single oral dose of ^{14}C-febuxostat 1 mg/kg in male rats (n = 3/time point), radioactivity levels peaked at 8 hours post-dose in the large intestine and at 1 hour post-dose in other tissues, and the radioactivity levels at 1 hour post-dose were higher (1.2- to 9.6-fold) in the stomach, small intestine, kidneys, liver, and bladder, in descending order of radioactivity, than in plasma. In most tissues, the radioactivity levels declined over time after reaching the peak, but even at 168 hours post-dose, the radioactivity detected was higher in the liver, kidneys, adrenal glands, lungs, small intestine, bladder, submandibular lymph nodes, submandibular gland, brown fat, pancreas, thymus, and epididymis, in descending order, than plasma and the mean fold ratios to plasma radioactivity level were 3.0- to 46.9.

Following a single oral dose of ^{14}C-febuxostat 1 mg/kg, or on Day 14 of a 14-day treatment with oral doses of ^{14}C-febuxostat 1 mg/kg qd in male rats (n = 3/time point), radioactivity levels peaked at 1 hour post-dose in most tissues. Radioactivity levels at 1 hour post-dose following a single dose were higher (1.4- to 6.3-fold) in the stomach, large intestine, small intestine, liver, and kidney, in descending order, and radioactivity levels on Day 14 of repeated dosing were higher (1.3- to 9.2-fold) in the stomach, small intestine, kidneys, liver, and bladder, in descending order, than in plasma. Both following a single dose and on Day 14 of repeated doses, the radioactivity levels declined over time after reaching the peak in most tissues; radioactivity was not detected in plasma from 96 hours post-dose, while it was detected in the liver, skin, kidneys, small intestine, spleen, adrenal glands, lungs, large intestine, stomach, submandibular lymph nodes, bone marrow, brown fat, bladder, submandibular gland, mesenteric lymph nodes, fat, pancreas, epididymis, heart, thymus, testis, skeletal muscles, and eyeballs (on Day 14 of repeated doses only) even at 168 hours post-dose. The mean ratio of $AUC_{0\text{-}24h}$ on Day 14 of repeated doses relative to AUC_{inf} following a single dose was 1.0 in plasma, 1.2 in the stomach, and <1.0 in other tissues.

Following a single oral dose of ^{14}C-febuxostat 1 mg/kg in pregnant rats (gestation day 19, n = 3/time point), the mean ratio of radioactivity levels relative to that in maternal plasma ranged from 0.16 to 0.45 in the placenta and from 0.01 to 0.03 in fetal liver and below the detection limit in fetal body at 1, 4, and 8 hours post-dose, while 1.79 in the placenta, 0.21 in fetal liver, and 0.50 in fetal body at 24 hours post-dose.

The mean protein binding (ultrafiltration method) of ^{14}C-febuxostat (0.5-50 μg/mL) in rat plasma ranged from 99.4% to 99.5%, and the mean plasma protein binding (ultrafiltration method) within the first 4 hours post-dose in rats that received a single intravenous dose of ^{14}C-febuxostat (1 mg/kg) or a single oral dose of ^{14}C-febuxostat (1-10 mg/kg) ranged from 98.7% to 99.6%. After a single oral dose and 14-day treatment with oral doses of ^{14}C-febuxostat 1 mg/kg qd in male rats (n = 3/time point), the distribution in blood cells (mean) up to 24 hours post-dose ranged from 1.6% to 20.0% following a single dose and from 0.0% to 29.9% on Day 14 of repeated doses. Following a single intravenous dose or a single oral dose of ^{14}C-febuxostat 1 mg/kg in male dogs (n = 3), the distribution in blood cells (mean) up to 12 and 24 hours post-dose ranged from 3.3% to 34.2% and from 12.7% to 45.7%, respectively [for human data, see "4.(ii).A.(1) *In vitro* studies in human biomaterials"].

3.(ii).A.(3) Metabolism (4.2.2.4-1 to 4.2.2.4-7, 4.2.2.4-9, and 4.2.2.4-13)

Metabolism of ^{14}C-febuxostat (25 μM) was evaluated in isolated hepatocytes of male and female mice, rats, and dogs. As a result, oxidative metabolites (67M-1, febuxostat hydroxylated at position 3 of isobutyl moiety; 67M-2, febuxostat hydroxylated at position 2 of isobutyl moiety; 67M-3, desbutylated febuxostat; 67M-4, dicarboxylic acid of febuxostat; all of these are active metabolites) and a glucuronide conjugate of unchanged febuxostat (67-G) were detected. In male mice and male and female rats, a glucuronide conjugate of 67M-3 (67M-3-G) was also detected. Metabolism of ^{14}C-febuxostat (25 μM)

was evaluated in liver microsomes of male mice, rats, and dogs. As a result, 67M-1 to 67M-4 were detected, and after addition of the coenzyme of UGT, 67-G and 67M-3-G were detected [for human data, see "4.(ii).A.(1) *In vitro* studies in human biomaterials"].

In mice (n = 6/sex/time point/administration route) that received a single intravenous dose of ^{14}C-febuxostat 1 mg/kg or a single oral dose of ^{14}C-febuxostat 3 mg/kg, unchanged febuxostat detected accounted for 91.4% to 96.5% (intravenous dose) and 86.4% to 95.5% (oral dose) of total plasma radioactivity at each time point up to 4 hours post-dose. Following a single intravenous dose of ^{14}C-febuxostat 1 mg/kg or a single oral dose of ^{14}C-febuxostat 3 mg/kg in mice (n = 12/sex/administration route), unchanged febuxostat was mainly detected (percentage of the administered radioactivity, 8.6%-21.6%) in urine in males while 67-G was mainly detected (0.1%-15.2%) in urine in females up to 24 hours post-dose irrespective of the administration route; unchanged febuxostat (15.5%-29.5%) and 67M-2 (8.4%-20.2%) were mainly detected in feces both in males and females irrespective of the administration route. A single intravenous dose of ^{14}C-febuxostat 1 mg/kg and a single oral dose of ^{14}C-febuxostat 3 mg/kg were administered to bile-duct-cannulated mice (n = 2-4/sex/administration route). As a result, 67-G (3.9%-58.9%) was mainly detected following an intravenous dose and unchanged febuxostat (1.8%-13.3%) and 67-G (1.9%-26.9%) were mainly detected following an oral dose in bile up to 24 hours post-dose both in males and females.

Following a single oral dose of ^{14}C-febuxostat 3 mg/kg in male rats (n = 3/time point), unchanged febuxostat and 67M-3 were mainly detected in plasma, and AUC_{inf} of unchanged febuxostat and 67M-3 accounted for 66.0% and 12.9% of, respectively, that of the total plasma radioactivity. In urine, 67M-1 and 67M-3 were mainly detected up to 24 hours post-dose (mean percentage of the administered radioactivity, 10.6% and 9.3%, respectively). In bile-duct-cannulated male rats (n = 3) that received a single oral dose of ^{14}C-febuxostat 1 mg/kg, 67-G was mainly detected (49.7%) in bile. In the liver of male rats (n = 3/time point) that received a single oral dose of ^{14}C-febuxostat 1 mg/kg, unchanged febuxostat was mainly detected at 1 and 24 hours post-dose, and their mean percentage relative to the radioactivity detected in the liver was 77.3% and 82.4%, respectively. In milk of lactating rats (lactation days 12-13, n = 3) that received a single oral dose of ^{14}C-febuxostat 1 mg/kg, unchanged febuxostat was mainly detected at 4 hours post-dose, and its mean percentage relative to the radioactivity detected in the milk was 78.8%.

In plasma of male dogs (n = 3/administration route) that received a single dose of ^{14}C-febuxostat 1 mg/kg intravenously or orally, unchanged febuxostat and 67M-3 were mainly detected. AUC_{inf} of unchanged febuxostat accounted for 47% (intravenous administration) and 50% (oral administration) and AUC_{inf} of 67M-3 accounted for 25% (intravenous administration) and 19% (oral administration) of that of the total plasma radioactivity. In urine up to 72 hours after intravenous or oral administration, 67M-1 was mainly detected, their mean percentage relative to the administered radioactivity was 2.6% and 2.1%, respectively.

Male rats (n = 4/group) received orally febuxostat 1 or 20 mg/kg qd for 7 days. As a result, a decrease in liver wet weight was observed in the 1 mg/kg group and a decrease in liver microsome protein content was observed in both dose groups, but no changes were observed in body weight, other protein content, or enzyme activity in either group.

3.(ii).A.(4) Excretion (4.2.2.2-1, 4.2.2.5-1 to 4.2.2.5-4)

Mice (n = 12/sex/administration route) received a single intravenous dose of ^{14}C-febuxostat 1 mg/kg or a single oral dose of ^{14}C-febuxostat 3 mg/kg. Radioactivity recovered in urine within 120 hours post-dose accounted for 20.7% and 20.2% (mean percentage of the administered radioactivity), respectively, in males, and 17.3% and 8.5%, respectively, in females; radioactivity recovered in feces accounted for 57.4% and 55.4%, respectively, in males, and 53.0% and 55.2%, respectively, in females. Bile-duct-cannulated mice (n = 3-4/sex/administration route) received a single intravenous dose of ^{14}C-febuxostat 1 mg/kg or a single oral dose of ^{14}C-febuxostat 3 mg/kg. Radioactivity recovered in bile within 24 hours post-dose accounted for 21.3% and 29.4%, respectively, in males, and 47.8% and 18.1%, respectively, in females.

In male rats (n = 5/administration route) that received a single dose of ^{14}C-febuxostat 1 mg/kg intravenously or orally, 47.7% and 34.0%, respectively, of the administered radioactivity were recovered in urine, and 46.6% and 53.5%, respectively, of the administered radioactivity were recovered in feces, within 168 hours post-dose. In male rats (n = 5) that received a single oral dose of ^{14}C-febuxostat 1 mg/kg, 37.7% and 59.4%, respectively, of the administered radioactivity were recovered in urine and feces, within 168 hours post-dose. In bile-duct-cannulated male rats (n = 5/administration route) that received a single dose of ^{14}C-febuxostat 1 mg/kg intravenously and orally, 57.2% and 52.2%, respectively, of the administered radioactivity were recovered in bile within 48 hours post-dose. In male rats (n = 5) that received orally ^{14}C-febuxostat 1 mg/kg qd for 14 days, 25.3% and 77.9%, respectively, of the administered radioactivity were recovered in urine and feces within 168 hours after the last dose. Radioactivity levels in plasma and milk of lactating rats (Lactation Day 14, n = 3/time point) following a single oral dose of ^{14}C-febuxostat 1 mg/kg peaked at 0.5 and 4 hours post-dose, respectively, and declined over time until 48 hours post-dose. The mean radioactivity concentration ratio (milk/plasma) was <1 within 0.5 hours post-dose, 1.79 and 4.51 at 1 and 2 hours post-dose, respectively, and 6.45 to 7.89 at ≥4 hours post-dose.

In male dogs (n = 3/administration route) that received a single dose of ^{14}C-febuxostat 1 mg/kg intravenously or orally, 9.1% and 5.6%, respectively, of the administered radioactivity were recovered in urine and 85.1% and 89.7%, respectively, of the administered radioactivity were recovered in feces within 168 hours post-dose.

3.(ii).A.(5) PK studies in 5/6 nephrectomized rats (4.2.2.7-1 and 4.2.2.7-2)

A single intravenous dose of ^{14}C-febuxostat 0.5 mg/kg (n = 3/group) or ^{14}C-allopurinol 0.5 mg/kg (n = 4/group) was administered to 5/6 nephrectomized male rats and sham-operated male rats. After administration of ^{14}C-febuxostat, the total body clearance (CL) of total serum radioactivity (mean ± SD) was 168.4 ± 17.6 mL/h/kg in the sham operation group and 78.1 ± 6.4 mL/h/kg in the 5/6 nephrectomy group, and 45.8% and 28.0% on average of the administered radioactivity were recovered in urine within 24 hours post-dose in the respective groups. After administration of ^{14}C-allopurinol, the CL of total serum radioactivity was 398.4 ± 38.6 mL/h/kg in the sham operation group and 84.3 ± 8.6 mL/h/kg in the 5/6 nephrectomy group, 71.4% and 67.0%, respectively, of the administered radioactivity were recovered in urine within 24 hours post-dose in the sham and 5/6 nephrectomy groups.

3.(ii).B Outline of the review by PMDA

3.(ii).B.(1) Distribution to skin

PMDA asked the applicant to explain possible clinical relevance of the delayed clearance of radioactivity from the skin in the tissue distribution study of ^{14}C-febuxostat in rats with a discussion on the relation between the delayed clearance and the post-marketing information from overseas on the occurrence of skin and subcutaneous tissue disorders.

The applicant's response:

Adverse events classified as skin and subcutaneous tissue disorders reported in the second periodic safety update report (October 21, 2008 to April 20, 2009)[8] included rash generalised, swelling face, rash pruritic, urticaria, pruritus, and rash, but all of these events were non-serious. Although the clearance of radioactivity from the skin was slow ($t_{1/2}$ following a single oral dose was 50 hours and $t_{1/2}$ following 14-day repeated oral doses was 100 hours) in rats, the end-of-treatment examination in the rat 26-week repeat-dose toxicity study revealed no notable skin-related findings similar to those described in the above post-marketing report in any male or female animals including the vehicle control animals. On the basis of above findings, there is least relationship between the delayed clearance of radioactivity from rat skin seen after administration of ^{14}C-febuxostat and the occurrence of skin and subcutaneous tissue disorders described in the post-marketing report, and therefore, the delayed elimination from rat skin does not suggest any potential problems of clinical significance.

PMDA asked the applicant to explain the melanin affinity of febuxostat.

[8] During this survey period, febuxostat was administered to patients for approximately 3 months (February to April, 2009) after approval in the U.S.

The applicant's response:
Melanin affinity was evaluated in a study of tissue distribution in pigmented rats conducted in the U.S. Although the above study also showed a slow clearance of febuxostat-derived radioactivity from the skin, febuxostat is not considered to have high melanin affinity because $t_{1/2}$ did not substantially differ between pigmented (313 hours) and non-pigmented (289 hours) skin and was 5.44 hours for clearance from the eye.

PMDA's view:
No sufficient data support the applicant's explanation that there is least relationship between the delayed clearance of radioactivity from the skin in the tissue distribution study of ^{14}C-febuxostat in rats and the occurrence of skin and subcutaneous tissue disorders described in the post-marketing report, and that the delayed elimination from rat skin does not suggest any potential problems of clinical significance. In addition, 3 and 6 serious skin and subcutaneous tissue disorders, respectively, were reported in the third and fourth periodic safety update reports (April 21, 2009 to April 20, 2010), and skin-related safety in humans will be additionally reviewed in the clinical section [see "4.(iii).B.(3).5) Skin-related adverse events"].

3.(ii).B.(2) PK studies in 5/6 nephrectomized rats
PMDA asked the applicant to explain the following findings obtained from the PK studies in 5/6 nephrectomized rats: the cumulative urinary excretion of total radioactivity up to 24 hours post-dose was lower in the 5/6 nephrectomy group (28.0%) than in the sham operation group (45.8%) after administration of ^{14}C-febuxostat, while it was comparable between the sham operation (71.4%) and the 5/6 nephrectomy (67.0%) groups after administration of ^{14}C-allopurinol.

The applicant's response:
Approximately 80% of the administered allopurinol is excreted in urine as an active metabolite in the form of oxypurinol (Hande KR, et al., *Am J Med.* 1984;76:47-56); therefore, the cumulative urinary excretion of total radioactivity up to 4 hours post-dose was lower in the 5/6 nephrectomy group (21.1%) than in the sham operation group (55.5%), while the cumulative urinary excretion up to 24 hours post-dose was comparable between the two groups due to very limited excretion by the other routes. After administration of ^{14}C-febuxostat, the cumulative urinary excretion of total radioactivity up to 4 hours post-dose (34.6% in the sham operation group, 17.9% in the 5/6 nephrectomy group) and up to 24 hours (45.8% in the sham operation group, 28.0% in the 5/6 nephrectomy group) were both lower in the 5/6 nephrectomy group, while it is inferred that the total radioactivity that could not be excreted in urine due to 5/6 nephrectomy was excreted by other routes such as bile.

PMDA's view:
It is unclear whether the total radioactivity that could not be excreted in urine due to 5/6 nephrectomy was excreted by other routes such as bile within 24 hours after administration of ^{14}C-febuxostat because total radioactivity in bile was not measured. However, PMDA accepted the applicant's response because the applicant's discussion described above is considered reasonable to some extent [for PK in humans with renal impairment, see "4.(ii).B.(1) PK and PD effects in patients with renal impairment"].

3.(iii) Summary of toxicology studies
3.(iii).A Summary of the submitted data
Toxicity studies of febuxostat conducted include single-dose toxicity, repeat-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, and other toxicity studies (antigenicity and mechanistic studies).

3.(iii).A.(1) Single-dose toxicity (4.2.3.1-1 and 4.2.3.1-3)
Single-dose toxicity was evaluated in oral toxicity studies in rats and dogs. In rats, findings included decreased locomotor activity, salivation, irregular respiration, decreased body temperature, involuntary urination, cloudy urine, and clonic convulsion and necropsy findings included yellow granular materials in the kidneys and bladder. In dogs, transient vomiting and then decreased locomotor activity, lateral position, diarrhea, salivation, and decreased body weight were observed. The approximate lethal dose was determined to be 300 to 600 mg/kg in rats and >2000 mg/kg in dogs.

3.(iii).A.(2) Repeat-dose toxicity

Repeat-dose toxicity was evaluated in oral toxicity studies in rats (for 5 and 26 weeks) and dogs (for 13 and 52 weeks). Major effects observed in rats and dogs included renal and bladder calculi, inflammatory changes in renal tubules and interstitium, and hyperplasia of renal pelvic and bladder transitional epithelium, and in rats alone, decreased thyroid hormone levels. While the renal and bladder calculi were attributed to xanthine produced by exaggerated pharmacological activity of febuxostat, xanthine calculi are considered unlikely to be formed in humans after administration of febuxostat based on the following facts: Daily urinary excretion of purine metabolite per body weight is higher in rodents than in humans (Hitchings GH, *Ann Rheum Dis.* 1966;25:601-607, Shimo T, et al. *Toxicol Pathol.* 2009;37:438-445); xanthine calculus has not been reported by patients receiving allopurinol, a similar drug, with the exception of patients with conditions such as Lesch-Nyhan syndrome, which is characterized by extremely greater purine metabolism; and urine volume is higher in humans than in rats and dogs (Hitchings GH, *Ann Rheum Dis.* 1966;25:601-607). AUC of febuxostat at the no observed adverse effect level (NOAEL) (12 mg/kg/day in rats in 26-week study, 15 mg/kg/day in dogs in 52-week study) was estimated to be 6.8 to 11.1 times that (7760.35 ng·h/mL) at the proposed maximum dose (60 mg/day) in rats and 4.1 to 5.0 time in dogs.

3.(iii).A.(2).1) Five-week repeat-dose toxicity study in rats (4.2.3.2-1)

Male and female rats received orally febuxostat 0 (vehicle[9]), 3, 15, 75, or 150 mg/kg qd for 5 weeks. Treatment-related deaths were observed in 1 of 20 males in the 75 mg/kg/day group and 2 of 20 males in the 150 mg/kg/day group. Globular granules in urinary sediment were observed in the ≥3 mg/kg/day groups; salivation and inflammatory changes in renal tubules and interstitium were observed in the ≥15 mg/kg/day groups; reduced body weight gain, decreased food consumption, increased water consumption, increased kidney weight, renal pelvic calculus, and hyperplasia of renal pelvic transitional epithelium, etc. were observed in the ≥75 mg/kg/day groups; and bladder calculus and hyperplasia of bladder transitional epithelium were observed in males at ≥75 mg/kg/day. In addition, electron microscopy of animals in the 150 mg/kg/day group showed a deposition of materials with high electron density in renal tubules. Furthermore, effects on the thyroid (thyroid hormone) including a decrease in triiodothyronine (T_3) in males in the ≥75 mg/kg/day groups and a decrease in thyroxine (T_4) in males in the 75 mg/kg/day group and in males and females in the 150 mg/kg/day group were observed. An increased thyroid weight and hyperplasia of thyroid follicular epithelium were observed in the ≥75 mg/kg/day groups, which were attributed to a persistent increase in thyroid-stimulating hormone (TSH) levels associated with decreased thyroid hormone levels. After a 4-week recovery period, changes in general symptoms, body weight, food consumption, the bladder, and thyroid were reversible, but water consumption and changes in the kidneys (e.g., crystal deposition in renal tubules, renal pelvic calculus, inflammatory changes in renal tubules and interstitium, and hyperplasia of renal pelvic transitional epithelium) were not reversible. Analyses by thin-layer chromatography and Fourier transform infrared spectroscopy identified the main component of the observed globular granules in urinary sediment as xanthine; and thus, the observed renal and bladder calculi were considered to be caused by xanthine produced by exaggerated pharmacological activity of febuxostat, and hyperplasia of renal pelvic and bladder transitional epithelium were attributed to mechanical stimulation due to calculus. Taking into account the above discussion that xanthine crystal deposition/calculi are unlikely to occur in humans because the granules in urinary sediment and renal pelvic calculus observed in the 15 mg/kg/day group are minimal changes caused by the pharmacological activity of febuxostat, the NOAEL in this study was determined to be 15 mg/kg/day.

3.(iii).A.(2).2) Twenty-six-week repeat-dose toxicity study in rats (4.2.3.2-2)

Male and female rats received orally febuxostat 0 (vehicle[9]), 3, 12, or 48 mg/kg qd for 26 weeks. Treatment-related deaths were not observed. Salivation, globular or petal-shaped granules in urinary sediment, and renal pelvic calculus were observed in the ≥12 mg/kg/day groups; increased water consumption, inflammatory changes in renal tubules and interstitium, and hyperplasia of renal pelvic transitional epithelium, etc. were observed in the 48 mg/kg/day group; and a trend towards increased thyroid weight, bladder calculus, and hyperplasia of vesical transitional epithelium were observed in males in the 48 mg/kg/day group. After a 6-week recovery period, salivation, granules in urinary sediment, bladder calculus, and hyperplasia of bladder transitional epithelium were reversible. Taking

[9] 0.5% MC solution

into account the above discussion that xanthine crystal deposition/calculi are unlikely to occur in humans because the granules in urinary sediment and renal pelvic calculus observed in the 12 mg/kg/day group are minimal changes caused by the pharmacological activity of febuxostat, the NOAEL in this study was determined to be 12 mg/kg/day.

3.(iii).A.(2).3) Thirteen-week repeat-dose toxicity study in dogs (4.2.3.2-3)

Male and female dogs received orally febuxostat 0, 5, 20, or 80 mg/kg qd for 13 weeks. Globular granules in urinary sediment, renal pelvic calculus, hyperplasia of renal pelvic transitional epithelium, bladder calculus, and hyperplasia of bladder transitional epithelium were observed in the ≥20 mg/kg/day groups; and urinary occult blood, dilatation of renal tubules, and cellular infiltration in the kidney, etc. were observed in the 80 mg/kg/day group. After a 6-week recovery period, cellular infiltration in the kidneys, renal pelvic calculus, and hyperplasia of renal pelvic transitional epithelium were not reversible. Taking into account the above discussion that xanthine crystal deposition/calculi are unlikely to occur in humans because the changes observed in the 20 mg/kg/day group are minimal changes caused by the pharmacological activity of febuxostat, the NOAEL in this study was determined to be 20 mg/kg/day.

3.(iii).A.(2).4) Fifty-two-week repeat-dose toxicity study in dogs (4.2.3.2-4)

Male and female dogs received orally febuxostat 0, 5, 15, or 45 mg/kg qd for 52 weeks. One of 6 male and 1 of 6 female animals in the 45 mg/kg/day group were sacrificed moribund due to progress in severity of clinical signs (e.g., hunched position, brown urine, and decreased body temperature). Globular granules in urinary sediment, urinary occult blood, and renal pelvic calculus were observed in the ≥15 mg/kg/day groups. Salivation, yellow cloudy urine, increased kidney weight, dilatation of renal pelvis, bladder calculus, submucosal cellular infiltration in the renal pelvis, hyperplasia of renal pelvic and bladder transitional epithelium, clinical chemistry findings included increases in urea nitrogen and creatinine were observed in the 45 mg/kg/day group. After a 13-week recovery period, changes in clinical signs, urinalysis, clinical chemistry, and organ weight measurements were reversible, but renal pelvic calculus, dilatation of renal pelvis, submucosal cellular infiltration in the renal pelvis, and hyperplasia of renal pelvic transitional epithelium were not reversible. Taking into account the above discussion that xanthine crystal deposition/calculi are unlikely to occur in humans because the changes observed in the 15 mg/kg/day group are minimal changes caused by the pharmacological activity of febuxostat, the NOAEL in this study was determined to be 15 mg/kg/day.

3.(iii).A.(3) Genotoxicity

Genotoxicity was evaluated in *in vitro* studies including a bacterial reverse mutation assay, a chromosomal aberration assay in Chinese hamster lung (CHL) cells, a human lymphocyte chromosomal aberration assay, and a gene mutation assay in mouse lymphoma cells, and *in vivo* studies including a mouse bone marrow micronucleus assay, an unscheduled DNA synthesis assay in rat hepatocytes, and a rat bone marrow chromosomal aberration assay. Short-term treatment yielded positive results in the chromosomal aberration assay in CHL cells, but all the other results were negative; therefore, febuxostat was considered not to be biologically genotoxic.

3.(iii).A.(4) Carcinogenicity

Carcinogenicity was evaluated in 104-week repeated oral dose toxicity studies in mice and rats, and the incidence of bladder transitional cell papilloma and carcinoma was increased in female mice and male rats. In rodents, long-term mechanical stimulation such as that due to calculus causes epithelial hyperplasia leading to cancer (Ito N, *Tr. Soc. Pathol. Jpn.* 1986;75:3-37, Fukushima S, et al., *Cancer Res.* 1992;52:1675-1680, Shirai T, et al., *Carcinogensis.* 1995;16:501-505, Okumura M. et al., *Carcinogenesis.* 1992;13:1043-1045). Thus, taking into account the above discussion that xanthine crystal deposition/calculi are unlikely to occur in humans because the proliferative changes (hyperplasia of renal pelvic, bladder, and urethral transitional epithelium, and bladder transitional cell papilloma and carcinoma) in the carcinogenicity studies are caused by xanthine crystal deposition/calculi resulting from exaggerated pharmacological activity of febuxostat, the neoplastic changes observed in rodents were considered unlikely to occur in humans. AUC of febuxostat at the non-carcinogenic dose (7.5 mg/kg/day in female mice, 12 mg/kg/day male rats) was estimated to be 4.9 times that (7760.35 ng·h/mL) at the proposed maximum dose (60 mg/day) in female mice and 8.6 times in male rats.

3.(iii).A.(4).1) Carcinogenicity studies in mice (4.2.3.4.1-6 and 4.2.3.4.1-7)

Male and female B6C3F$_1$ mice received orally febuxostat 0 (vehicle[9]), 3, 7.5, or 18.75 mg/kg qd for 104 weeks. In females in the 18.75 mg/kg/day group, an increase in the incidence of bladder transitional cell papilloma (0 of 50, 0 of 50, 0 of 50, and 3 of 50 females in the respective dose groups) and bladder transitional cell carcinoma (0 of 50, 0 of 50, 0 of 50, and 1 of 50 in the respective dose groups) was observed, but a Fisher's exact test showed no statistically significant difference. Non-neoplastic lesions observed included edema, lymphocytic infiltration, and fibrosis of the bladder, hyperplasia of bladder transitional epithelium, and renal fibrosis and calculus in females, and urethral calculus in males in the 18.75 mg/kg/day group.

3.(iii).A.(4).2) Carcinogenicity studies in rats (4.2.3.4.1-8 and 4.2.3.4.1-9)

Male and female F344 rats received orally febuxostat 0 (vehicle[9]), 3, 6, 12, or 24 mg/kg qd for 104 weeks. The incidence of bladder transitional cell papilloma (0 of 50 animals, 0 of 50 animals, 0 of 50 animals, 0 of 50 animals, 10 of 50 animals) and bladder transitional cell carcinoma (0 of 50 animals, 0 of 50 animals, 0 of 50 animals, 0 of 50 animals, 7 of 50 animals) were increased in males in the 24 mg/kg/day group. Non-neoplastic lesions observed included hyperplasia of bladder transitional epithelium in males in the 12 mg/kg/day group and males and females in the 24 mg/kg/day group, urethral (males) and renal calculi in the ≥12 mg/kg/day groups, and bladder calculus (males), interstitial nephritis, hyperplasia of renal pelvic transitional epithelium (males and females), urethral calculus/cellular infiltration/transitional epithelium hyperplasia (males), and localized hyperplasia of the parathyroid gland (males) in the 24 mg/kg/day group; the localized hyperplasia of the parathyroid gland was considered to be a change (secondary hyperparathyroidism) caused by febuxostat-related chronic renal failure.

3.(iii).A.(5) Reproductive and developmental toxicity

Reproductive and developmental toxicity was evaluated in a fertility study in rats, embryo-fetal development studies in rats and rabbits, and a pre- and postnatal development and maternal function study in rats. No febuxostat-related effects on the reproductive function of parent animals or teratogenic effects were observed. In the pre- and postnatal development and maternal function study in rats, effects observed on F_1 pups included yellowish-white granules in the kidneys, ureter, and bladder, a trend towards increased thyroid weight, and growth inhibition (e.g., a reduction in weaning rate, reduced body weight gain, and delayed eyelid opening). The maternal AUC of febuxostat at the NOAEL for F_1 pups was estimated to be 2.1 times the AUC (7760.35 ng·h/mL) of febuxostat at the proposed maximum dose (60 mg/day). Febuxostat was shown to have a low placental transfer (4.2.2.3-7) and be excreted in milk (4.2.2.5-4) in rats.

3.(iii).A.(5).1) Pre-pregnancy and early pregnancy study in rats (4.2.3.5.1-1)

Febuxostat 0 (vehicle[9]), 3, 12, or 48 mg/kg qd was administered orally to male rats from 64 days prior to mating until the day before necropsy and to female rats from 15 days prior to mating until gestation day 7. Yellowish-white granular materials were observed in the kidneys in the 48 mg/kg/day group, and yellowish-white granular materials in the bladder and an increased thyroid weight in males in the 48 mg/kg/day group, but no effects were observed on sperm test findings, copulation rate, conception rate, oestrous cycle, number of corpora lutea of pregnancy, number of implantation sites, number of live fetuses, fetal weight, or embryo-fetal lethality. The NOAEL in this study was determined to be 12 mg/kg/day for general toxicity of parent animals and 48 mg/kg/day for reproductive function of parent animals and embryos/fetuses.

3.(iii).A.(5).2) Embryo-fetal development study in rats (4.2.3.5.2-1)

Febuxostat 0 (vehicle[9]), 3, 12, or 48 mg/kg qd was administered orally to pregnant rats during gestation days 7 to 17. Yellowish-white granular materials in the kidneys were observed in maternal animals in the 48 mg/kg/day group, but no effects of febuxostat were observed on maternal reproductive function or embryos/fetuses. The NOAEL in this study was determined to be 12 mg/kg/day for maternal general toxicity and 48 mg/kg/day for maternal reproductive function and embryos/fetuses.

3.(iii).A.(5).3) Embryo-fetal development study in rabbits (4.2.3.5.2-2)

Febuxostat 0 (vehicle[9]), 3, 12, or 48 mg/kg qd was administered orally to pregnant rabbits during gestation days 6 to 18. Abortion was observed in 1 of 21 maternal animals each in the 3 and 48

mg/kg/day groups. The 2 animals showed inappetence from several days before the abortion. Because the incidence of abortion in rabbits has known to be increased by restricting food consumption (Matsuzawa T, et al., *Toxicology.* 1981;22:255-259), these findings of abortion were attributed to the inappetence. No statistically significant decrease was observed in food intake in any dose groups, and the inappetence in the 2 animals was considered unrelated to febuxostat. No external, visceral, or skeletal abnormalities or those in fetal survival or development were found. The NOAEL in this study was determined to be 48 mg/kg/day for maternal general and reproductive toxicities and for embryos/fetuses.

3.(iii).A.(5).4) Rat study of pre- and postnatal development, including maternal function (4.2.3.5.3-1)

Febuxostat 0 (vehicle[9]), 3, 12, or 48 mg/kg qd was administered orally to pregnant rats from Gestation Day 7 to Lactation Day 20. One of 24 maternal animals died and 1 of 24 maternal animals was sacrificed moribund due to difficult parturition in the 48 mg/kg/day group. Reduced body weight gain, decreased food intake, and yellowish-white granules in the kidneys and bladder were observed in the ≥12 mg/kg/day groups; and increased kidney and thyroid weights and an increase in the number of dams with total litter loss were observed in the 48 mg/kg/day group. The maternal death, difficult parturition, and increase in the number of dams with total litter loss were considered attributed to deterioration in the general condition of maternal animals caused by xanthine crystal deposition/calculi in the kidneys due to the pharmacological activity of febuxostat. Among F_1 pups, postweaning deaths and moribund animals were observed in 1 of 48 males and 1 of 48 females in the 12 mg/kg/day group and in 5 of 33 males in the 48 mg/kg/day group; yellowish-white granules in the kidneys, ureter, and bladder were observed in the ≥12 mg/kg/day groups; findings including a trend towards increased thyroid weight, a reduction in weaning index, reduced body weight gain, delayed eyelid opening, and delayed cleavage of the balanopreputial gland were observed in the 48 mg/kg/day group. These findings were considered to be effects on the kidneys and growth inhibition associated with decreased thyroid hormone levels caused by exposure to febuxostat via milk and their related changes. No external or skeletal effects, or those on function test, learning performance, or reproductive function were observed in F_1 pups. The NOAEL in this study was determined to be 3 mg/kg/day for maternal general toxicity, 12 mg/kg/day for maternal reproductive function, and 3 mg/kg/day for F_1 pups.

3.(iii).A.(6) Other toxicity studies

Other toxicity studies included antigenicity studies and mechanistic studies.

3.(iii).A.(6).1) Antigenicity

(a) Antigenicity study in mice (4.2.3.7.1-1)

Male mice were sensitized by intraperitoneal injections (a total of 2 injections, 4 weeks apart) of febuxostat with aluminum hydroxide gel, and sera collected 14 days after the last sensitization were intradermally injected into untreated rats to induce passive cutaneous anaphylactic (PCA) reaction. As a result, no PCA reactions were observed in the febuxostat-sensitized group, showing that febuxostat has no antigenic potential.

(b) Antigenicity study in guinea pigs (4.2.3.7.1-2)

Male guinea pigs were sensitized by subcutaneous injections (a total of 3 injections, 7 days apart) of febuxostat with Freund's complete adjuvant, and 15 days after the last sensitization, received intravenously febuxostat for active systemic anaphylaxis (ASA) test. In addition, sera collected 14 days after the last sensitization were intradermally injected into untreated guinea pigs to induce PCA reaction. As a result, neither ASA nor PCA reactions were observed in the febuxostat-sensitized group, showing that febuxostat has no antigenic potential.

3.(iii).A.(6).2) Mechanistic studies

(a) One-month repeat-dose toxicity study in mice fed with urinary pH modifying-diet (4.2.3.7.7-1 and 4.2.3.7.7-2)

Febuxostat 0 (vehicle[9])[10] or 250 mg/kg qd was administered orally for 4 weeks to male and female mice fed with a (1) normal diet; (2) urinary pH modifying-diet (Altromin 1321); (3) urinary pH modifying-diet (normal diet containing sodium bicarbonate); (4) urinary pH modifying-diet (normal diet containing

[10] Vehicle group animals were fed with a normal diet or urinary pH modifying-diet (Altromin 1321).

calcium carbonate); (5) diet prepared by adding sodium chloride to each urinary pH modifying-diet; or (6) diet containing sodium chloride to normal diet. Tubulointerstitial nephritis developed in all febuxostat groups. The occurrence of renal tubulointerstitial nephritis was not decreased in animals fed with a urinary pH modifying-diet, or with those prepared by adding sodium chloride to urinary pH modifying-diet. Male animals that were fed with a normal diet and received febuxostat showed bladder calculus, the major component of which was identified as xanthine by X-ray analysis and Fourier transform infrared spectroscopy, and hyperplasia of bladder transitional epithelium. The bladder calculus was reduced among animals fed with urinary pH modifying-diet, or with those prepared by adding sodium chloride to urinary pH modifying-diet, and no bladder epithelium hyperplasia was observed in any groups. The proliferative changes in transitional epithelium of the urinary tract (renal pelvis, bladder, and urethra) in the repeat-dose toxicity and carcinogenicity studies were considered to be caused by long-term mechanical stimulation due to xanthine crystal deposition/calculi formed by exaggerated pharmacological activity of febuxostat.

(b) Rat 5-week repeated oral dose toxicity study evaluating thyroid hormonal changes (4.2.3.7.7-3)

Male rats received orally febuxostat 0 (vehicle[9]) and 150 mg/kg qd for 5 weeks. A febuxostat-related increase in plasma TSH, decreases in free T_3 and T_4, increased thyroid weight, and hyperplasia and hypertrophy of thyroid follicular epithelium were observed, but all these changes were suppressed by concomitant subcutaneous injection of T_4 50 μg/kg qd.

3.(iii).B Outline of the review by PMDA

3.(iii).B.(1) Effects on the thyroid

PMDA asked the applicant to discuss the effects on the thyroid seen in rats.

The applicant's response:

Based on the results from the rat 5-week repeated oral dose toxicity study evaluating thyroid hormonal changes, the hypertrophy of the thyroid and hyperplasia of thyroid follicular epithelium in rats are attributed to a persistent increase in TSH levels associated with decreased thyroid hormone levels. Although the mechanism of the decrease in thyroid hormone levels in rats is unclear at present, the effects of febuxostat on the thyroid are rat-specific changes and febuxostat is unlikely to cause thyroid hormonal changes in humans based on the following facts: Rats, in which thyroxine-binding globulin (TBG) is not expressed and $t_{1/2}$ of thyroid hormones is short, are considered sensitive to homeostatic perturbations of the thyroid (Larsson M, et al., *General and Comparative Endocrinology.* 1985;58:360-375, Hooth MJ, et.al., *Toxicologic Pathology.* 2001;29:250-259); in the carcinogenicity study in rats, no changes were observed in the thyroid even after 2 years of febuxostat administration at approximately 25- to 26-fold the human exposure; and no changes were observed in the thyroid in the repeat-dose toxicity study in dogs, in which TBG is expressed like in humans.

Since there is a concern about effects of febuxostat, which is highly excreted in milk, during the developmental period, when sensitivity to thyroid hormones is high, PMDA asked the applicant to discuss the risk in humans.

The applicant's response:

Although febuxostat administered during the period up to fetal organogenesis had no effects on the embryos/fetuses in the reproductive and developmental toxicity studies, growth inhibition considered attributable to decreased thyroid hormone levels primarily due to exposure to febuxostat via milk was observed in the study of pre- and postnatal development, including maternal function. Thyroid hormones are essential for child's development, and decrease in thyroid hormone levels during the developmental period has been reported to induce developmental disorder of the brain and behavior disability (Axelstad M, et al., *Toxicology and Applied Pharmacology.* 2008;232:1-13). However, febuxostat is not considered to decrease thyroid hormone levels to such an extent as to cause developmental disorder of the brain in newborn rats because no effects of febuxostat were observed on behavior/function, learning performance, or reproductive function and because the observed increase in thyroid weight in newborns was mild as compared with toxicity data with propylthiouracil, an antithyroid drug (Propacil Tablets 50 mg [interview form]). In addition, since the effects of febuxostat on thyroid hormones are considered to be changes specific to rats, which lack TBG, febuxostat is very unlikely to affect human newborns.

However, given that febuxostat was shown to be excreted in milk in rats and that the safety of febuxostat in breastfed infants has not been demonstrated, a precautionary statement that women receiving febuxostat should avoid breastfeeding along with findings in the rat study of pre- and postnatal development, including maternal function will be included in the draft package insert.

PMDA's view:
The mechanism of the decrease in thyroid hormone levels is unclear, and the effects on the thyroid in humans will be additionally reviewed in the clinical section [see "4.(iii).B.(3).3) Thyroid function-related adverse events"]. Since the applicant took appropriate actions on PMDA's instruction to include an appropriate precautionary statement regarding the observed reproductive and developmental toxicity associated with decreased thyroid hormone levels (growth inhibition of newborns) in the package insert, there are no particular toxicological problems.

3.(iii).B.(2) Xanthine crystals/calculi
PMDA asked the applicant to discuss the risk associated with xanthine crystals/calculi in the urinary tract in patients with overproduction type hyperuricemia, in whom urinary urate excretion is elevated.

The applicant's response:
Hyperuricemia is broadly classified into "underexcretion type," "overproduction type," and "mixed type." Urinary urate excretion in patients with overproduction type hyperuricemia has been reported to be approximately 1.3 times that in patients with normal type hyperuricemia (The Guideline Revising Committee of Japanese Society of Gout and Nucleic Acid Metabolism eds. *Guideline for the management of hyperuricemia and gout*, 2nd ed. [*Japanese Treatment Guideline* 2nd ed.]). Given that urinary excretion of purine metabolites is approximately 40 and 7 times that in humans, respectively, in rats and dogs (Hitchings GH, *Ann Rheum Dis.* 1966;25:601-607, Shimo T, et al. *Toxicol Pathol.* 2009;37:438-445), and that urine volume is lower and urinary xanthine concentration is higher in rats and dogs than in humans, xanthine crystals/calculi such as those seen in rats and dogs are unlikely to be formed in patients with hyperuricemia, even when the elevated urinary urate excretion in patients with overproduction type hyperuricemia is taken into consideration.

PMDA accepted the applicant's response.

3.(iii).B.(3) Nephrotoxicity
In the 1-month repeat-dose toxicity study in mice fed with a urinary pH modifying-diet, animals with no calculi in the kidneys or bladder developed tubulointerstitial nephritis. PMDA asked the applicant to explain the mechanism of tubulointerstitial nephritis and discuss the relevant risk in humans.

The applicant's response:
Although the mechanism of the tubulointerstitial nephritis seen in this study is unclear, formation and dissolution of xanthine crystals/calculi are assumed to proceed simultaneously in the renal tubular lumen when animals are fed with a urinary pH modifying-diet. This leads to transient formation of xanthine crystals/calculi in renal parenchyma and repeated inflammatory reactions, finally inducing the tubulointerstitial nephritis. In addition, renal tubular lesions (e.g., crystalline deposits, dilatation of renal tubules) and interstitial fibrosis have been observed also in xanthine oxidoreductase-deficient mice (Ohtsubo T, et al., *Hypertension.* 2009;54:868-876), and tubulointerstitial nephritis in the study is considered to be caused by xanthine crystals formed in renal tubular lumen. The incidence of adverse events of renal/urinary calculus was low in all Japanese and foreign clinical studies conducted. No dose-dependency in the incidence was observed in foreign long-term treatment studies (Studies C02-021 and TMX-[redacted]-005). No clear effects were observed on laboratory parameters related to renal tubular function (β_2-microglobulin [MG] and β-N-acetyl-D-glucosaminidase [NAG]). Therefore, febuxostat is unlikely to affect renal function in humans.

PMDA's view:
The effects of febuxostat on renal function in humans, including the above points, will continue to be reviewed in the clinical section [see "4.(iii).B.(3).2) Kidney/bladder-related adverse events"].

3.(iii).B.(4) Phototoxicity

PMDA asked the applicant to explain the phototoxicity of febuxostat.

The applicant's response:
Among the photochemical properties of febuxostat, photoabsorption was characterized by ultraviolet spectrophotometry, and febuxostat exhibits the absorption at 215 and 314 nm. However, no toxicological findings were observed that suggested phototoxicity to the eye or skin in the 26-week repeat-dose toxicity study in rats, 52-week repeat-dose toxicity study in dogs, or carcinogenicity studies. Although 1 event of photosensitivity reaction for which a causal relationship to febuxostat could not be ruled out was reported in a foreign long-term treatment study (Study C02-021, reference data), it was mild in severity, and no events of photosensitivity reaction classified as skin and subcutaneous tissue disorders have been contained in Japanese clinical study data and foreign post-marketing data; therefore, febuxostat is unlikely to be phototoxic.

PMDA's view:
Since non-clinical studies were not conducted to evaluate phototoxicity despite the presence of ultraviolet absorption by febuxostat, the safety in humans related to photosensitivity reactions will continue to be reviewed in the clinical section [see "4.(iii).B.(3).5) Skin-related adverse events"].

4. Clinical data

4.(i) Summary of biopharmaceutic studies and associated analytical methods

4.(i).A Summary of the submitted data

As the biopharmaceutic evaluation data, the applicant submitted data, namely the results from Japanese clinical studies (Studies TMX-67-[redacted] and TMX-67-[redacted]), a foreign clinical study (Study TMX-[redacted]-018), and dissolution tests (Studies TMX-[redacted]002F, TMX-[redacted]002F, TMX-67/[redacted]/01/R, TMX-67/[redacted]/02, and TMX-[redacted]-A).

Human biomaterials obtained from Japanese clinical studies were quantified by HPLC-fluorescence detection (for determination of unchanged febuxostat in plasma, and unchanged febuxostat and its metabolites [67M-1, 67M-2, and 67M-4] in urine), LC-MS/MS (for determination of febuxostat metabolites [67M-1, 67M-2, and 67M-4] in plasma), and HPLC/ultraviolet-visible spectrophotometry (for determination of urate, xanthine, and hypoxanthine in plasma and urine). The lower limits of quantification in plasma and urine were 4 ng/mL and 4 ng/mL, respectively, for unchanged febuxostat, 0.5 or 5 ng/mL and 100 ng/mL, respectively, for metabolites, 10 μM or 0.168 mg/dL and 100 μM or 1.68 mg/dL, respectively, for urate, 1 μM or 0.0152 mg/dL and 5 μM or 0.76 μg/mL, respectively, for xanthine, and 1 μM or 0.0136 mg/dL and 5 μM or 0.68 μg/mL, respectively, for hypoxanthine. Primary study results are shown below.

4.(i).A.(1) Clinical PK and food effect studies of the final product formulation (5.3.1.1-1, Study TMX-67-[redacted] [[redacted] to [redacted] 20[redacted]])

An open-label, parallel-group comparative study (PK study of the final product formulation) along with an open-label, two-treatment, two-period crossover study (food effect study) were conducted in Japanese healthy adult male subjects to evaluate the PK, PD effects, and safety of the final product formulation along with the effect of food on the PK and PD effects.

In the PK study of the final product formulation, subjects received a single oral dose of febuxostat 10 mg (one 10 mg tablet), 20 mg (one 20 mg tablet), or 40 mg (two 20 mg tablets) in the morning under fasted conditions. In the food effect study, subjects received a single oral dose of febuxostat 40 mg (two 20 mg tablets) in the morning under fasted conditions or after breakfast in Step 1 or 2. Washout period between treatments was 7 days.

All 32 treated subjects (24 in the PK study of the final product formulation, 16 in the food effect study[11]) were included in PK, PD, and safety analyses.

[11] The data obtained from 8 subjects who had received the final product formulation under fasted conditions in the food effect study were used as data for the 40 mg group (8 subjects) in the PK study of the final product.

PK parameters of unchanged febuxostat in the PK study of the final product formulation are shown in Table 2. C_{max} and AUC increased with increasing dose, and t_{max}, CL/F, MRT, Vdss/F, $t_{1/2}$, and Vd_{β}/F remained almost constant irrespective of dose level. In urine, ≥95% of unchanged febuxostat excreted within the first 96 hours post-dose was excreted by 24 hours post-dose, and CLr accounted for 2.1% to 3.6% of CL/F. The mean C_{max} and AUC_{inf} of oxidative metabolites (67M-1, 67M-2, and 67M-4) ranged from 0.90% to 1.41% and from 0.92% to 2.06%, respectively, of those of unchanged febuxostat, and the mean C_{max} and AUC_{inf} of 67-G ranged from 10.07% to 18.89% and from 14.80% to 25.30%, respectively, of those of unchanged febuxostat. The mean $fe_{0\text{-}96h}$ of oxidative metabolites (67M-1, 67M-2, and 67M-4) and 67-G ranged from 2.19% to 5.53% and from 49.03% to 51.61%, respectively. In urine, ≥95% of metabolites (67M-1, 67M-2, 67M-4, and 67-G) excreted within the first 96 hours post-dose were excreted before 24 hours post-dose, and the mean CLr of metabolites (67M-1, 67M-2, 67M-4, and 67-G) ranged from 9820 to 26,137 mL/h. The mean t_{min} (time to reach the minimum concentration) of plasma urate was 13.25 to 18.00 hours; the plasma urate level at 24 hours post-dose was decreased from baseline by means of 7.59% (10 mg group), 14.35% (20 mg group), and 22.75% (40 mg group). The mean t_{max} of plasma xanthine was 6.00 to 8.25 hours; the plasma xanthine levels returned nearly to baseline at 48 hours post-dose. The mean t_{max} of plasma hypoxanthine was 2.00 to 2.38 hours; the plasma hypoxanthine levels were decreased below baseline at 8 to 12 hours post-dose, and almost remained constant at or below baseline at ≥24 hours post-dose. After administration of febuxostat, urinary urate excretion was decreased while those of xanthine and hypoxanthine were increased.

Table 2. PK parameters of unchanged febuxostat following single oral dose

Parameter	10 mg (n = 8)	20 mg (n = 8)	40 mg (n = 8)
t_{max} (h)	1.38 ± 1.06	1.31 ± 0.46	1.19 ± 0.84
C_{max} (ng/mL)	496.24 ± 165.95	1088.31 ± 178.92	2270.28 ± 866.68
AUC_{obs} (ng·h/mL)	1476.20 ± 432.10	3175.36 ± 689.06	6952.60 ± 1384.63
AUC_{inf} (ng·h/mL)	1537.04 ± 430.88	3296.24 ± 751.87	7085.21 ± 1341.22
CL/F (L/h)	6.900 ± 1.634	6.338 ± 1.382	5.820 ± 1.047
MRT (h)	5.26 ± 0.57	5.43 ± 1.03	5.53 ± 0.81
Vdss/F (L)	36.771 ± 10.718	33.473 ± 4.655	31.686 ± 4.971
$t_{1/2}$ (h)	6.21 ± 0.92	6.20 ± 1.10	7.29 ± 1.79
β (1/h)	0.11368 ± 0.01531	0.11494 ± 0.01882	0.10073 ± 0.02843
Vd_{β}/F (L)	62.894 ± 20.937	55.878 ± 12.883	59.729 ± 11.881
$fe_{0\text{-}96h}$ (%)	3.85 ± 2.08	2.18 ± 0.45	2.74 ± 1.87
CLr (mL/h)	251.15 ± 99.33	134.54 ± 26.46	160.56 ± 113.87

Mean ± SD

MRT, Mean residence time; Vdss/F, Steady-state volume of distribution;

β, Slope of elimination phase; Vd_{β}/F, Elimination phase volume of distribution; fe, Urinary excretion ratio (amount excreted in urine/total amount administered); CLr, Renal clearance

In the food effect study, the geometric mean ratios (fed/fasted) [two-sided 90% confidence interval (CI)] of C_{max} and AUC_{inf} of unchanged febuxostat were 0.72 [0.61, 0.84] and 0.82 [0.77, 0.86], respectively, representing decreases in C_{max} and AUC_{inf} by approximately 28% and 18%, respectively, after administration under fed conditions. The mean t_{max} in the fed group occurred 0.6 hours later than that in the fasted group. After administration under fasted and fed conditions, the mean C_{min} (minimum concentration) of plasma urate was 4.060 and 3.911 mg/dL, respectively, the rate of change in C_{min}[12] was -23.43% and -26.48%, respectively, the mean $C_{mean,\ 48h}$ (mean concentration during the first 48 hours post-dose) of plasma urate was 4.417 and 4.390 mg/dL, respectively, the mean C_{max} of plasma xanthine was 0.1713 and 0.1612 mg/dL, respectively, the mean $C_{mean,\ 48h}$ of plasma xanthine was 0.0898 and 0.0883 mg/dL, respectively, the mean C_{max} of plasma hypoxanthine was 0.1455 and 0.1480 mg/dL, respectively, and the mean $C_{mean,\ 48h}$ of plasma hypoxanthine was 0.0683 and 0.0800 mg/dL, respectively; urinary urate excretion within 24 hours post-dose was 422.23 and 491.44 mg, respectively, that of xanthine was 131.18 and 131.54 mg, respectively, and that of hypoxanthine was 45.62 and 37.53 mg, respectively.

Five adverse events (blood triglycerides increased, abdominal pain lower/diarrhoea [2 events], and blood triglycerides increased) were reported by 3 of 24 subjects in the PK study of the final product formulation, and 7 adverse events (abdominal pain lower/diarrhoea [2 events], diarrhoea, and blood triglycerides increased in the fasted group; 2 events of diarrhoea reported by separate subjects in the

[12] $\{(C_{min}$ - baseline concentration)/(beseline concentration)$\} \times 100$ (%)

postprandial group) were reported by 5 of 32 subjects in the food effect study; all these events were mild in severity.

4.(i).A.(2) Phase I study (food effect after single oral dose) (5.3.1.1-2, Study TMX-67-[to 19])

A randomized, open-label, three-period crossover study was conducted in Japanese healthy adult male subjects to evaluate the food effect on the PK and safety of a single oral dose of febuxostat.

Subjects received febuxostat 12.5 mg under fasted conditions, 30 minutes before a meal, or 30 minutes after a meal at the first, second, or third dose. Washout period between doses was 7 days.

All 12 treated subjects were included in safety analysis. Of these, 1 subject was withdrawn from the study before receiving the third dose (to be administered 30 minutes after the meal) due to an adverse event. As a result, the PK/PD analysis set included 12 subjects who received febuxostat under fasted conditions and 30-minute before a meal, and 11 subjects who received under 30-minute after a meal.

PK analysis showed that the mean plasma C_{max} and $AUC_{0\text{-}24h}$ of unchanged febuxostat were 571.6 ng/mL and 1503.9 ng·h/mL, respectively, after fasted administration, 570.9 ng/mL and 1347.4 ng·h/mL, respectively, after preprandial administration, and 388.9 ng/mL and 1259.7 ng·h/mL, respectively, after postprandial administration, and C_{max} was decreased by approximately 32% after postprandial administration and $AUC_{0\text{-}24h}$ was decreased by approximately 10% after preprandial administration and by approximately 16% after postprandial administration as compared with those after fasted administration.

PD analysis showed that the decrease in plasma urate levels was smallest after fasted administration, while comparable between after preprandial and postprandial administration. The increase in plasma xanthine levels was largest after fasted administration, while comparable between after preprandial and postprandial administration.

Three adverse events were reported by 2 subjects after fasted administration, 4 adverse events were reported by 2 subjects after preprandial administration, and 1 adverse event was reported by 1 subject after postprandial administration. One subject experienced after preprandial administration 3 adverse events (blood urine present, red blood cells urine positive, and protein urine present; all were moderate in severity) for which a causal relationship to the study drug could not be ruled out (adverse drug reactions) and the subject was withdrawn from the study.

4.(i).A.(3) Dissolution test comparing the final product formulations (5.3.1.2-4 and 5.3.1.2-6, Study TMX-67/ /02 [20 to 20]; TMX- -A [20 to 20])

According to the "Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms" (PMSB/ELD Notification No. 64 dated February 14, 2000, partially amended by PFSB/ELD Notification No. 1124004 dated November 24, 2006), the level of formulation change between 10 and 20 mg tablets of the final product formulation is C, and that between 20 and 40 mg tablets is A. Bioequivalence was demonstrated by dissolution testing for both cases.

4.(i).A.(4) Relative bioavailability study between Teijin Pharma and Abbott products (5.3.1.2-5, Study TMX- -018 [to 20])

A randomized, open-label, four-period crossover study was conducted in non-Japanese healthy adult subjects (target sample size, 28 subjects) to compare bioavailability of Abbott B1 20 mg tablet with that of Teijin Pharma 20 mg tablet and between four Abbott B1 20 mg tablets and one Abbott B1 80 mg tablet, and to evaluate dose-proportionality over the dose range of 20 to 80 mg. Comparison of bioavailability between Teijin Pharma and Abbott products is described below.

Subjects received a single oral dose of one Teijin Pharma 20 mg tablet or one Abbott B1 20 mg tablet in the morning under fasted conditions. Washout period between treatments was ≥6-day.

All 28 treated subjects were included in safety analysis; of these, 26 subjects were included in PK analysis. Excluded were 2 subjects who withdrew from the study (consent withdrawal and personal reasons).

PK analysis showed that the geometric mean ratios (Abbott/Teijin Pharma) [two-sided 90% CI] of C_{max} and AUC_t of unchanged febuxostat were 0.96 [0.84, 1.08] and 0.97 [0.92, 1.02], respectively.

Adverse events were reported by 5 subjects in the Teijin Pharma product group and 8 subjects in the Abbott product groups. For both products, adverse event reported by ≥2 subjects in both groups was injection site haemorrhage[13] (4 subjects in the Teijin Pharma product group, 2 subjects in the Abbott product groups).

4.(ii) Summary of clinical pharmacology studies

4.(ii).A Summary of the submitted data

The applicant submitted evaluation data, namely the results from Japanese clinical studies (Studies TMX-67-[redacted], TMX-67-[redacted], TMX-67-[redacted], TMX-67-[redacted], TMX-67-[redacted], TMX-67-[redacted], TMX-67-[redacted], TMX-67-[redacted], TMX-67-[redacted], and TMX-67-[redacted]). In addition, the applicant submitted reference data, namely the results from foreign clinical studies (Studies C[redacted]-040, TMX-[redacted]-001, TMX-[redacted]-016, TMX-[redacted]-008, TMX-[redacted]-012, C[redacted]-005, C[redacted]-013, TMX-[redacted]-006, C[redacted]-006, TMX-[redacted]-014, TMX-[redacted]-017, C03-059, C03-057, F-P[redacted]-162, C[redacted]-023, and TMX-67_101). Additionally, the results from *in vitro* studies in human biomaterials (5.3.2.1-1 to 5.3.2.1-4 and 5.3.2.2-1 to 5.3.2.2-18) were submitted. Primary study results are shown below. Because some Japanese studies were completed ≥10 years earlier, the applicant examined the storage status of source documents at all study sites prior to submitting the current application. As a result, 5 subjects (2 in Study TMX-67-[redacted], 2 in Study TMX-67-[redacted], 1 in Study TMX-67-[redacted]) were identified as not linked to their medical records or informed consent forms. During the current review, PMDA confirmed both results obtained from data including and excluding these subjects, and has concluded that there is no particular problem with describing study results of Study TMX-67-[redacted] with the data of these subjects excluded in this Review Report.

4.(ii).A.(1) *In vitro* studies using human biomaterials (5.3.2.1-3, 5.3.2.1-4, 5.3.2.2-1, 5.3.2.2-2, and 5.3.2.2-11 to 5.3.2.2-18)

The mean protein binding (ultrafiltration method) of ^{14}C-febuxostat (0.4-10 μg/mL) in human plasma was 97.8% to 99.0%, and the mean protein bindings of ^{14}C-febuxostat (0.1-100 μg/mL) to human serum albumin (40 mg/mL) and human α_1-acid glycoprotein (1 mg/mL) were 98.9% to 99.1% (bound at diazepam site) and 3.2% to 15.9% (nonspecific binding), respectively. The mean protein binding of ^{14}C-febuxostat (0.4-10 μg/mL) in human plasma in the presence of warfarin (10 μg/mL), digoxin (0.005 μg/mL), ibuprofen (20 and 200 μg/mL), captopril (0.8 and 8 μg/mL), bezafibrate (3.5 and 35 μg/mL), verapamil (0.1 and 1.0 μg/mL), and nitrendipine (0.1 and 1.0 μg/mL) ranged from 97.2% to 98.9%. In addition, the plasma protein bindings of ^{14}C-warfarin (10 μg/mL), ^{3}H-ibuprofen (20 and 200 μg/mL), ^{3}H-verapamil (0.1 and 1.0 μg/mL), and ^{3}H-nitrendipine (0.1 and 1.0 μg/mL) in the presence of febuxostat (0.4-10 μg/mL) were compared with those in the absence of febuxostat. As a result, a significant decrease in the plasma protein binding was observed for verapamil (from 86.2% down to 80.8% at 0.1 μg/mL, 89.5% to 85.0% at 1.0 μg/mL) and nitrendipine (89.8% to 85.2% at 0.1 μg/mL, 91.4% to 88.4% at 1.0 μg/mL) in the presence of 10 μg/mL of febuxostat.

Evaluation of metabolism of ^{14}C-febuxostat (25 μM) in isolated human hepatocytes revealed formation of 67M-1 to 67M-4 and 67-G, and evaluation of metabolism of ^{14}C-febuxostat (25 μM) using human liver microsomes showed the presence of 67M-1 to 67M-4 and, after addition of the coenzyme of UGT, showed the presence of 67-G. Metabolic reaction to form 67M-2 from febuxostat (100 μM) in human liver microsomes was found to be suppressed by 52.5%, 55.9%, and 66.4% on average, respectively, in the presence of antibodies to CYP1A2, CYP2C8, and CYP2C9 (rabbit antisera), as compared with that in the presence of rabbit serum. Evaluation in human CYP- and UGT-expressing microsomes suggested that CYP2C9 is primarily involved in formation of 67M-1, CYP1A1 and CYP1A2 are primarily involved in formation of 67M-2, CYP1A1 is primarily involved in formation of 67M-3, and UGT1A1, UGT1A8, UGT1A9, UGT1A7, UGT1A3, UGT2B7, and UGT1A10 are primarily involved in formation

[13] E.g., bruise at the venous puncture site

of 67-G. Evaluation of inhibition of CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5) by febuxostat (1-100 μM for CYP2B6, 20-80 μM for CYP2C8, 50 and 100 μM for other isoforms) in human liver microsomes revealed an inhibition of CYP2C8 and CYP2D6 with Ki values of 20 and 40 μM, respectively. Evaluation of induction of CYP isoforms (CYP1A1/2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5) by febuxostat (3-300 μM) in primary human hepatocytes revealed no concentration-dependent induction.

4.(ii).A.(2) Human PK and PD studies

4.(ii).A.(2).1) PK and PD in healthy adult subjects

(a) Phase I study (single oral dose study) (5.3.3.1-1, Study TMX-67-[redacted] [redacted] 19[redacted] to [redacted] 19[redacted])

A single-blind study was conducted in Japanese healthy adult male subjects to evaluate the safety, tolerability, and PK of a single oral dose of febuxostat.

Subjects received a single dose of febuxostat 0.2, 0.8, 3.2, 6.25, 12.5, 25, or 50 mg in Steps 1 to 7, respectively, in the morning under fasted conditions. In each Step, 8 subjects were randomly assigned to febuxostat (n = 6) and placebo (n =2).

All 56 treated subjects were included in PK, PD, and safety analyses.

PK analysis showed the following: the plasma unchanged febuxostat levels were below the lower limit of quantification at all time points in the 0.2 mg group; the plasma C_{max} and AUC of unchanged febuxostat increased less than dose-proportionally at ≤6.25 mg and increased dose-proportionally at ≥12.5 mg in the 0.8 to 50 mg groups; the mean t_{max} was 0.7 to 1.3 hours; and the mean $t_{1/2}$ was 2.3 hours in the 0.8 mg group, 3.3 hours in the 3.2 mg group, and 5.4 to 5.8 hours in the 6.25 to 50 mg groups. In the 0.2 to 50 mg groups, the mean urinary excretion rate within the first 96 hours post-dose ranged from 0.0% to 3.8% for unchanged febuxostat, and 31.7% to 49.4% for unchanged febuxostat and 67-G combined.

PD analysis showed that the plasma urate levels were significantly decreased and plasma xanthine levels were significantly increased as compared with those immediately before administration in subjects receiving ≥3.2 mg. The urinary excretion of xanthine and hypoxanthine (collectively referred to as oxypurine) was increased with increasing dose.

A total of 46 adverse events were reported by 26 subjects (13 events in 9 subjects in the placebo group, 4 events in 4 subjects in the 0.8 mg group, 10 events in 2 subjects in the 3.2 mg group, 2 events in 2 subjects in the 6.25 mg group, 8 events in 5 subjects in the 12.5 mg group, 1 event in 1 subject in the 25 mg group, 8 events in 3 subjects in the 50 mg group); all these events were mild or moderate in severity.

(b) Phase I study (single oral high-dose study) (5.3.3.1-2, Study TMX-67-[redacted] [redacted] to [redacted] 20[redacted])

A randomized, double-blind, placebo-controlled study was conducted in Japanese healthy adult male subjects to evaluate the safety, tolerability, PK, and PD effects of a single oral dose of febuxostat up to 160 mg.

Subjects received a single dose of febuxostat 80, 120, or 160 mg in Steps 1 to 3, respectively, in the morning under fasted conditions. In each Step, 8 subjects were randomly assigned to febuxostat (n = 6) and placebo (n = 2).

All 24 treated subjects were included in PD and safety analyses, and of these, 18 subjects who received febuxostat were included in PK analysis.

PK parameters of unchanged febuxostat are shown in Table 3. A power model analysis showed a dose-proportional increase in plasma C_{max} and a more than dose-proportional increase in plasma AUC_{inf} of unchanged febuxostat in the 80 to 160 mg groups, and a mean t_{max} of 0.9 to 2.7 hours and a mean $t_{1/2}$ of 5.9 to 6.9 hours.

Table 3. PK parameters of unchanged febuxostat following single oral dose

Parameter	80 mg (n = 6)	120 mg (n = 6)	160 mg (n = 6)
t_{max} (h)	1.92 ± 1.02	0.92 ± 0.38	2.67 ± 1.37
C_{max} (ng/mL)	3765.25 ± 1008.34	7078.22 ± 2102.99	8240.27 ± 1325.03
AUC_{inf} (ng·h/mL)	13,300.47 ± 3032.31	23,430.77 ± 2066.89	38,905.63 ± 7963.33
$t_{1/2}$ (h)	6.90 ± 1.82	5.85 ± 1.52	6.55 ± 2.32

Mean ± SD

PD parameters are shown in Table 4. The plasma urate lowering activity in the 120 mg group was higher than that in the 80 mg group, but comparable to that in the 160 mg group. The plasma $AUC_{0\text{-}24h}$ of xanthine was slightly increased with increasing dose. The urinary excretions of urate and oxypurine were decreased and increased, respectively, as compared with those in the placebo group.

Table 4. PD parameters of unchanged febuxostat following single oral dose

Parameter	Placebo (n = 6)	80 mg (n = 6)	120 mg (n = 6)	160 mg (n = 6)
Rate of change in $C_{mean,\ 24h}$ of plasma urate (%)	2.10 ± 2.01	-20.27 ± 1.96	-24.40 ± 1.44	-23.58 ± 3.34
$AUC_{0\text{-}24h}$ (mg·h/mL) of plasma xanthine	0.3708 ± 0.0236	3.5753 ± 0.3159	3.9880 ± 0.2945	4.0182 ± 0.2872
Urinary urate excretion (mg) (within 24 hours post-dose)	583.48 ± 78.54	408.30 ± 36.49	346.35 ± 118.27	411.62 ± 32.58
Urinary oxypurine excretion (mg) (within 24 hours post-dose)	19.45 ± 3.30	194.83 ± 29.63	186.70 ± 64.08	224.05 ± 14.14

Mean ± SD

A total of 18 adverse events were reported by 7 subjects as follows: 6 events in 1 subject in the placebo group (aspartate aminotransferase [AST] increased/blood creatine phosphokinase [CK] increased/blood lactate dehydrogenase [LDH] increased/urine potassium increased/urine chloride increased/urine electrolytes increased); 2 events in 2 subjects in the 80 mg group (urinary beta 2 microglobulin [β_2-MG] increased and blood thyroid stimulating hormone [TSH] increased); 4 events in 1 subject in the 120 mg group (urine potassium increased/urine chloride increased/urine electrolytes increased [2 events]); and 6 events in 3 subjects in the 160 mg group (AST increased/blood CK increased, blood glucose increased, and haematocrit decreased/haemoglobin decreased/red blood cell count decreased). All these events were mild in severity.

(c) Phase I study (multiple oral dose study) (5.3.3.1-3, Study TMX-67-[redacted] [redacted] 19[redacted] to [redacted] 19[redacted])

A randomized, single-blind, placebo-controlled study was conducted in Japanese healthy adult male subjects to evaluate the safety, tolerability, and PK of multiple oral doses of febuxostat.

Subjects received placebo or febuxostat 12.5 mg qd after breakfast, or placebo or febuxostat 12.5 mg twice daily (bid) after morning and evening meals for 7 days.

All 20 treated subjects (8 in the 12.5 mg qd group, 7 in the 12.5 mg bid group, 5 in the placebo group) were included in PK, PD, and safety analyses.

The mean plasma PK parameters of unchanged febuxostat in the 12.5 mg qd group on Days 1 and 7, respectively, were as follows: C_{max}, 337.0 and 467.5 ng/mL; $AUC_{0\text{-}24h}$, 1352.0 and 1405.7 ng·h/mL; and $t_{1/2}$, 4.9 and 5.7 hours. The mean plasma PK parameters of unchanged febuxostat in the 12.5 mg bid group on Days 1 and 7, respectively, were as follows: C_{max} after the morning meal, 325.7 and 451.2 ng/mL; C_{max} after the evening meal, 278.1 and 257.4 ng/mL; $AUC_{0\text{-}10h}$ after the morning meal, 1114.4 and 1296.9 ng·h/mL; $AUC_{10\text{-}24h}$ after the evening meal, 1450.1 and 1278.6 ng·h/mL; and $t_{1/2}$, 2.6 to 4.4 hours.

PD analysis showed that the mean C_{min} of plasma urate and mean C_{max} of plasma xanthine on Day 7 were 3.786 and 0.0991 mg/dL, respectively, in the 12.5 mg qd group, 2.976 and 2.847 mg/dL, respectively, after the morning meal in the 12.5 mg bid group, and 0.1736 and 0.1731 mg/dL, respectively, after the evening meal in the 12.5 mg bid group.

A total of 37 adverse events were reported by 16 subjects (11 events in 3 subjects in the placebo group, 14 events in 7 subjects in the 12.5 mg qd group, 12 events in 6 subjects in the 12.5 mg bid group); all these events were mild in severity.

(d) Phase I study (additional multiple oral dose study) (5.3.3.1-4, Study TMX-67-[redacted] [redacted] 19[redacted])
A randomized, single-blind, placebo-controlled study was conducted in Japanese healthy adult male subjects to evaluate the safety, tolerability, and PK of multiple oral doses of febuxostat.

Subjects received placebo or febuxostat 25 mg qd after breakfast for 7 days.

All 11 treated subjects (8 in the febuxostat group, 3 in the placebo group) were included in PK, PD, and safety analyses.

PK analysis showed that the mean plasma C_{max} of unchanged febuxostat on Days 1 and 7 was 712.5 and 812.1 ng/mL, respectively, and the mean plasma $AUC_{0\text{-}24h}$ of unchanged febuxostat on Days 1 and 7 was 2480.3 and 3096.6 ng·h/mL, respectively.

PD analysis showed that the mean C_{min} of plasma urate on Days 1 and 7 was 4.285 and 3.490 mg/dL, respectively, and the mean C_{max} of plasma xanthine on Days 1 and 7 was 0.1776 and 0.2068 mg/dL, respectively.

A total of 5 adverse events were reported by 3 subjects (3 events in 2 subjects in the placebo group, 2 events in 1 subject in the febuxostat group); all these events were mild in severity.

(e) Phase I study (multiple oral high-dose study) (5.3.3.1-5, Study TMX-67-[redacted] [redacted] 20[redacted] to [redacted] 20[redacted])
A randomized, double-blind, placebo-controlled study was conducted in Japanese healthy adult male subjects to evaluate the safety, tolerability, PK, and PD effects of multiple oral doses of febuxostat up to 160 mg qd and multiple oral doses of febuxostat up to 60 mg bid.

Subjects in the qd group received febuxostat 40, 80, 120, or 160 mg qd after breakfast in Steps 1-1 to 1-4, respectively, and subjects in the bid group received febuxostat 20, 40, or 60 mg bid after morning and evening meals in Steps 2-1 to 2-3, respectively, for 7 days. In each Step, 8 subjects were randomly assigned to febuxostat (n = 6) and placebo (n = 2).

All 56 treated subjects were included in PD and safety analyses, and of these, 42 subjects who received febuxostat were included in PK analysis.[14]

The mean plasma PK parameters of unchanged febuxostat in the 40 to 160 mg qd groups ranged as follows: C_{max} ratio (Day 7/Day1), 1.06 to 1.67; AUC ratio ($AUC_{0\text{-}24h}$ on Day 7/$AUC_{0\text{-}24h}$ on Day 1), 1.14 to 1.22; and $t_{1/2}$, 5.5 to 9.7 hours. The mean AUC ratio ($AUC_{0\text{-}10h}$ on Day 7/$AUC_{0\text{-}10h}$ on Day 1) in the 20 to 60 mg bid groups ranged from 1.32 to 1.40. On the basis of the plasma unchanged febuxostat concentration-time profile before morning dose on Days 2 to 7, a steady state was assumed to be reached on Day 3 both in the qd and bid groups. The plasma $AUC_{0\text{-}24h}$ ratio (each metabolite/unchanged febuxostat) on Days 1 and 7 in the 40 and 160 mg qd groups ranged from 1.4% to 1.8% for 67M-1, 2.5% to 3.0% for 67M-2, 1.7% to 2.8% for 67M-4, and 19.1% to 27.0% for 67-G. The mean daily urinary excretion rate in the 40 mg qd group on Days 1 to 7 was 1.3% to 1.8% for unchanged febuxostat, 4.9% to 5.3% for 67M-1, 4.9% to 6.1% for 67M-2, 2.6% to 3.2% for 67M-4, and 38.9% to 47.0% for 67-G.

PD analysis showed that the rate of change in $C_{mean,\ 24h}$ of plasma urate in subjects in the qd groups was greater in the 80 mg group than in the 40 mg group, and that it was comparable between the 80, 120, and 160 mg groups. The plasma $C_{mean,\ 24h}$ of xanthine in the qd groups increased with increasing dose up to 120 mg, and it was comparable between the 120 and 160 mg groups. The rate of change in $C_{mean,\ 24h}$ of plasma urate was smaller in the 40 mg qd group than in the 20 mg bid group. In the qd groups, the

[14] Due to the mix-up of collection tubes that occurred during blood sampling immediately before the morning dose on Day 2 of Step 2-1, the data of plasma concentrations of study drug, and data of urate, xanthine, and hypoxanthine in plasma at this time point obtained from all of the 8 subjects were excluded from the analysis.

urinary urate excretion was smaller in the 80 mg group than in the 40 mg group, and comparable in the ≥80 mg groups; the urinary oxypurine excretion increased with increasing dose up to 120 mg, and it was comparable between the 120 and 160 mg groups.

A total of 37 adverse events were reported by 17 subjects (8 events in 4 subjects in the placebo group, 1 event in 1 subject in the 40 mg qd group, 5 events in 3 subjects in the 80 mg qd group, 8 events in 1 subject in the 120 mg qd group, 2 events in 2 subjects in the 160 mg qd group, 4 events in 2 subjects in the 20 mg bid group, 3 events in 1 subject in the 40 mg bid group, 6 events in 3 subjects in the 60 mg bid group); all were mild in severity except for 1 moderate event each of rhinitis and alanine aminotransferase (ALT) increased reported by separate subjects in the 60 mg bid group.

(f) Metabolism and excretion (5.3.3.1-7, Study C[redacted]-040 [[redacted] to[redacted] 20[redacted]], Reference data)

An open-label study was conducted in non-Japanese healthy adult male subjects to evaluate metabolism and excretion of a single oral dose of ^{14}C-febuxostat.

Subjects received a single dose of ^{14}C-febuxostat 80 mg under fasted conditions.

All 6 treated subjects were included in PK[15] and safety analyses.

PK analysis showed that AUC_{inf} of unchanged febuxostat accounted for 82.7% of AUC_{inf} of total plasma radioactivity, and that the mean proportion of radioactive metabolites to total plasma radioactivity at each time point up to 4 hours post-dose ranged from 2.3% to 6.8% for 67-G, 1.1% to 4.4% for 67M-1, 0.8% to 5.5% for 67M-2, and 0.0% to 1.3% for 67M-4. The mean ratio (plasma/blood) of radioactivity concentration at 0.5, 3, 12, and 24 hours post-dose ranged from 1.4 to 1.6. A mean of 49.1% of administered radioactivity was recovered in urine and a mean of 44.9% of administered radioactivity in feces within the first 216 hours post-dose. In urine, within the first 48 hours post-dose, the radioactivity recovered accounted for 1.1% to 3.5% (the range of individual values) of administered radioactivity for unchanged febuxostat; 25.9% to 37.1% of administered radioactivity for 67-G, 2.5% to 7.1% of administered radioactivity for 67M-1; 3.9% to 7.3% of administered radioactivity for 67M-2; and 0.1% to 3.1% of administered radioactivity for 67M-4. In feces, within the first 120 hours post-dose, the radioactivity recovered accounted for 7.8% to 15.8% of administered radioactivity for unchanged febuxostat; 0.4% to 1.0% of administered radioactivity for 67-G; 3.6% to 7.1% of administered radioactivity for 67M-1; 3.7% to 6.7% of administered radioactivity for 67M-2; and 7.8% to 15.0% of administered radioactivity for 67M-4.

Five adverse events (conjunctivitis, flatulence/diarrhoea/hyperhidrosis, and toothache) were reported by 3 subjects, and all events were mild in severity.

(g) Study of QTc interval prolongation effect (5.3.4.1-1, Study C[redacted]-023 [[redacted] to [redacted] 20[redacted]], Reference data)

A randomized, four-period crossover study[16] was conducted in non-Japanese healthy adult subjects to evaluate the effects of multiple oral doses of febuxostat on QTc interval prolongation.

In Period 1, 2, 3, and 4, subjects received placebo, moxifloxacin 400 mg (positive control), febuxostat 80 mg, or febuxostat 300 mg qd for 4 days. Washout period between treatments was 7 days.

All 44 treated subjects were included in safety analysis, and of these, 41 subjects were included in electrocardiographic analysis. Excluded were 3 subjects who withdrew from the study (consent withdrawal, personal reasons, and elevation of laboratory values). Subjects for whom PK parameters were able to be calculated were included in PK analysis.

PK analysis showed that the mean plasma t_{max} and C_{max} of unchanged febuxostat on Day 4 were 2.4 hours and 2.46 μg/mL, respectively, in the febuxostat 80 mg group (n = 43) and 2.8 hours and 10.41 μg/mL, respectively, in the febuxostat 300 mg group (n = 41).

[15] One subject who was withdrawn from the study after sampling on Day 7 due to personal reasons was excluded from the summary data for total radioactivity in urine and feces.

[16] Placebo and febuxostat were administered in a double-blinded fashion, and moxifloxacin was administered in an unblinded fashion.

Electrocardiography revealed that the upper bound of the 90% CI of the difference from placebo in the maximum QT_{Fc} after administration and overall mean QT_{Fc} on Day 4 was <10 msec in both the febuxostat 80 and 300 mg groups and >10 msec in the moxifloxacin group.

One subject was withdrawn from the study due to adverse drug reactions (increases in amylase [moderate] and lipase [severe] after 4 days of treatment with febuxostat 80 mg).

4.(ii).A.(2).2) PK and PD in patients

(a) Study of circadian variation of serum urate levels and PK in patients with hyperuricemia (5.3.4.2-4, Study TMX-67-[redacted] [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label study was conducted in Japanese patients with hyperuricemia (including gout) to evaluate the circadian variation of serum urate levels, PK, and safety after administration of febuxostat.

Subjects received febuxostat 10 mg qd (induction dose) after breakfast for 2 weeks, and then 20 mg qd (maintenance dose) after breakfast for 4 weeks.

All 10 treated subjects were included in analyses of PK, circadian variation of serum urate levels, and safety.

The mean plasma PK parameters of unchanged febuxostat at Week 4 of maintenance treatment were as follows: C_{max}, 541.8 ng/mL; AUC_{obs}, 2092.3 ng·h/mL; t_{max}, 2.2 hours; and $t_{1/2}$, 8.2 hours. The ratio of mean plasma C_{max} (oxidative metabolites [67M-1, 67M-2, 67M-4]/unchanged febuxostat) ranged from 0.9% to 1.5%.

Evaluation of circadian variation of serum urate levels revealed that the difference between the minimum and maximum values of mean serum urate level at each time point[17] ranged from 8.37 mg/dL (at 20 hours pre-dose) to 9.11 mg/dL (immediately pre-dose) before induction treatment, and 5.51 mg/dL (at 8 hours post-dose) to 6.40 mg/dL (at 24 hours post-dose) at Week 4 of maintenance treatment.

Ten adverse events were reported by 4 subjects, and all events were mild in severity except for 2 events of moderate gastrointestinal upset reported by 1 subject.

(b) Early phase II clinical study (additional study including a 40 mg group) (5.3.4.2-3, Study TMX-67-[redacted] [[redacted] to [redacted] 20[redacted]])

An open-label study was conducted in Japanese patients with hyperuricemia (including gout) to explore the clinically effective dose of febuxostat.

Subjects received febuxostat 5 mg qd (induction dose) after breakfast for 2 weeks, and then 40 mg qd (maintenance dose) after breakfast for 6 weeks.

All 15 treated subjects were included in efficacy and safety analyses.

The change (mean ± SD) in plasma urate levels from baseline to Week 8, the primary efficacy endpoint, was -3.63 ± 1.18 mg/dL.

A total of 47 adverse events were reported by 15 subjects, and the following 8 adverse drug reactions were reported by 5 subjects: eosinophil percentage increased, diarrhoea, ALT increased, AST increased/ALT increased/gamma-glutamyltransferase [γ-GTP] increased/alkaline phosphatase [ALP] increased, and somnolence. Gout attack was reported by 3 subjects.

[17] Time points before induction treatment included 24, 22, 20, 18, 16, and 12 hours before treatment and immediately before treatment; time points at Week 4 of maintenance treatment included immediately before treatment and 2, 4, 6, 8, 12, and 24 hours after treatment.

4.(ii).A.(2).3) PK and PD effects in special populations

(a) Clinical pharmacology study in patients with renal impairment (single oral dose study) (5.3.3.3-2, Study TMX-67-[redacted])

An open-label study was conducted in Japanese subjects with normal renal function and patients with renal impairment to evaluate the effects of renal impairment on the PK, PD effects, and safety of a single oral dose of febuxostat.

Subjects received a single dose of febuxostat 20 mg within 30 minutes after breakfast.

All 14 treated subjects (4 with normal renal function, 5 with mild renal impairment,[18] 5 with moderate renal impairment[19])[20] were included in PK, PD, and safety analyses.

The ratios of mean plasma PK parameters of unchanged febuxostat in patients with mild and moderate renal impairment, respectively, to the corresponding PK parameters in subjects with normal renal function were as follows: t_{max}, 2.3 and 2.5; C_{max}, 0.54 and 0.60; AUC_{obs}, 0.82 and 1.41; and $t_{1/2}$, 1.2 and 1.8. When unchanged febuxostat and its oxidative metabolites were combined, the ratios were 0.55 and 0.61, respectively, for the mean C_{max} and 0.83 and 1.42, respectively, for the mean AUC_{obs}. The ratio of renal clearance of unchanged febuxostat was 0.91 and 0.42, respectively.

The ratios of mean PD parameters in patients with mild and moderate renal impairment, respectively, to those in subjects with normal renal function were as follows: ΔAUC[21] of plasma urate, 2.0 and 1.9; ΔAUC[22] of plasma xanthine, 1.1 and 1.9; urinary urate excretion, 0.98 and 0.69; urinary xanthine excretion, 0.87 and 0.70; urinary hypoxanthine excretion, 0.83 and 0.51; and urinary oxypurine excretion, 0.97 and 0.70.

Adverse events were reported only in patients with renal impairment. Those included constipation (1 event in 1 patient with mild renal impairment) and headache, upper respiratory tract inflammation, and nausea (1 event each in separate patients with moderate renal impairment); nausea was considered to be an adverse drug reaction. All these adverse events were mild in severity.

(b) PK study in patients with renal impairment (multiple oral dose study) (5.3.3.3-3, Study TMX-67-[redacted])

An open-label study was conducted in Japanese subjects with normal renal function and patients with renal impairment to evaluate the effects of renal impairment on the PK, PD effects, and safety of multiple oral doses of febuxostat.

Subjects received febuxostat 20 mg qd at 30 minutes after breakfast (only as a guide) for 7 days.

All 29 treated subjects were included in safety analysis, and of these, 21 subjects (9 with normal renal function,[23] 5 with mild renal impairment,[24] 7 with moderate renal impairment[25])[26] were included in PK and PD analyses. Excluded were 8 subjects (1 with total serum protein of ≤6.0 g/dL at the examination before enrollment, 5 who underwent C_{CR} measurement with inadequate procedures on the day before the first dose, 2 whose PK/PD evaluation may have been affected by change in concomitant medication/therapy).

PK analysis showed that the mean plasma protein binding (ultrafiltration method)[27] and plasma unbound fraction of unchanged febuxostat were 99.40% and 0.60%, respectively, in subjects with

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18 Including 1 patient with gout and 1 patient with hyperuricemia

19 Including 4 patients with hyperuricemia

20 Classified into the following 3 groups according to creatinine clearance (C_{CR}) at enrollment: subjects with normal renal function, C_{CR} ≥80 mL/min; patients with mild renal impairment, C_{CR} ≥50 to <80 mL/min; patients with moderate renal impairment, C_{CR} ≥30 to <50 mL/min).

21 Baseline concentration × 48 - $AUC_{0\text{-}48h}$

22 $AUC_{0\text{-}48h}$ - baseline concentration × 48

23 Including 3 patients with hyperuricemia

24 Including 3 patients with hyperuricemia

25 Including 3 patients with hyperuricemia

26 Classified into the following 3 groups according to 2-hour C_{CR} on the day before the start of treatment: subjects with normal renal function, C_{CR} ≥80 mL/min; patients with mild renal impairment, C_{CR} ≥50 to <80 mL/min; patients with moderate renal impairment, C_{CR} ≥30 to <50 mL/min).

27 Measured in plasma prepared from blood collected on the day before the start of treatment.

normal renal function, 99.34% and 0.66%, respectively, in patients with mild renal impairment, and 99.14% and 0.86%, respectively, in patients with moderate renal impairment. The plasma trough levels of unchanged febuxostat and its metabolites were found to be increased in patients with mild and moderate renal impairment as compared with those in subjects with normal renal function, but a steady state was apparently reached by Day 2 for unchanged febuxostat and by Day 7 for the metabolites. The PK parameters of unchanged febuxostat on Day 7 are shown in Table 5.

Table 5. PK parameters of unchanged febuxostat on Day 7 of multiple oral doses of febuxostat 20 mg

Parameter	Subjects with normal renal function (n = 9)	Patients with mild renal impairment (n = 5)		Patients with moderate renal impairment (n = 7)	
	Mean ± SD	Mean ± SD	Ratio of mean values[a)]	Mean ± SD	Ratio of mean values[a)]
t_{max} (h)	2.33 ± 1.66	3.80 ± 2.28	1.6	2.21 ± 1.35	0.9
C_{max} (ng/mL)	495.57 ± 157.64	504.06 ± 146.53	1.0	621.81 ± 270.93	1.3
$C_{max, u}$ (ng/mL)	2.95 ± 0.97	3.18 ± 0.77	1.1	5.24 ± 2.20	1.8
AUC_{0-24h} (ng·h/mL)	2123.43 ± 461.26	3238.09 ± 1088.82	1.5	3557.80 ± 1096.30	1.7
$AUC_{0-24h, u}$ (ng·h/mL)	12.65 ± 2.47	20.36 ± 6.22	1.6	30.31 ± 12.14	2.4
CL/F (L/h)	9.269 ± 1.765	6.300 ± 2.708	0.7	5.569 ± 2.258	0.6
CL_u/F (L/h)	1555.593 ± 332.398	950.429 ± 264.344	0.6	674.778 ± 282.583	0.4
$t_{1/2}$ (h)	6.89 ± 1.01	7.39 ± 2.10	1.1	8.18 ± 1.63	1.2
fe_{0-24h} (%)	1.86 ± 0.84	2.96 ± 1.25	1.6	2.81 ± 1.82	1.5
CLr (mL/h)	177.29 ± 78.48	202.62 ± 100.49	1.1	158.66 ± 91.69	0.9

$C_{max, u}$, C_{max} of unbound febuxostat (C_{max} × percent unbound fraction); $AUC_{0-24h, u}$, AUC_{0-24h} of unbound febuxostat (AUC_{0-24h} × percent unbound fraction); CL_u/F, CL/F of unbound febuxostat (dose level/$AUC_{0-24h, u}$)

a) Patients with renal impairment/subjects with normal renal function

The ratios of plasma PK parameters in patients with mild and moderate renal impairment, respectively, to those in subjects with normal renal function on Day 7 were as follows: C_{max} of unchanged febuxostat and its oxidative metabolites combined, 1.05 and 1.26; AUC_{0-24h} of unchanged febuxostat and its oxidative metabolites combined, 1.57 and 1.72; C_{max} of unchanged febuxostat, its oxidative metabolites and 67-G combined, 1.21 and 1.52; and AUC_{0-24h} of unchanged febuxostat, its oxidative metabolites and 67-G combined, 1.77 and 2.35.

PD parameters of unchanged febuxostat on Day 7 are shown in Table 6. The mean C_{CR} values on the day before the start of treatment and on Day 8 were 114.87 and 112.44 mL/h, respectively, in subjects with normal renal function, 64.89 and 58.66 mL/h, respectively, in patients with mild renal impairment, and 42.42 and 45.71 mL/h, respectively, in patients with moderate renal impairment.

Table 6. PD parameters of unchanged febuxostat on Day 7 of multiple oral doses of febuxostat 20 mg

Parameter		Subjects with normal renal function (n = 9)	Patients with mild renal impairment (n = 5)		Patients with moderate renal impairment (n = 7)	
		Mean ± SD	Mean ± SD	Ratio of mean values[a)]	Mean ± SD	Ratio of mean values[a)]
Plasma urate						
	Baseline level (mg/dL)	5.883 ± 0.887	6.284 ± 0.632	1.1	6.829 ± 1.890	1.2
	ΔAUC (mg·h/dL)	47.161 ± 12.001	46.593 ± 19.804	1.0	60.145 ± 27.811	1.3
	$C_{mean, 24h}$ (mg/dL)	3.918 ± 0.716	4.343 ± 1.100	1.1	4.323 ± 1.543	1.1
	Rate of change in $C_{mean, 24h}$ (%)	-33.491 ± 7.217	-31.268 ± 13.866	0.9	-36.768 ± 12.713	1.1
Urinary urate excretion (mg) (within 24 hours post-dose)		392.120 ± 98.240	288.589 ± 81.175	0.7	190.711 ± 67.383	0.5
Plasma xanthine						
	Baseline level (mg/dL)	0.0161 ± 0.0031	0.0184 ± 0.0035	1.1	0.0233 ± 0.0139	1.4
	ΔAUC (mg·h/dL)	1.8491 ± 0.5150	3.5373 ± 0.9157	1.9	4.1518 ± 1.3698	2.2
	$C_{mean, 24h}$ (mg/dL)	0.0932 ± 0.0206	0.1658 ± 0.0360	1.8	0.1963 ± 0.0571	2.1
Urinary xanthine excretion (mg) (within 24 hours post-dose)		110.006 ± 28.898	113.312 ± 49.178	1.0	70.257 ± 25.902	0.6

a) Patients with renal impairment/subjects with normal renal function

Two adverse events (nausea and rash) were reported by 2 subjects with normal renal function, 2 adverse events (dyspepsia and blood bilirubin increased) by 2 patients with mild renal impairment, and 3 adverse events (diarrhoea [2 events] and urinary β_2-MG increased) by 2 patients with moderate renal impairment; nausea and diarrhoea were considered to be adverse drug reactions. All events were mild in severity except for the event of moderate rash.

(c) Study of safety, PK, and PD effects in patients with renal impairment (5.3.3.3-4, Study TMX-[redacted]-008 [[redacted] to [redacted] 20[redacted]], Reference data)

An open-label, parallel-group comparative study was conducted in non-Japanese subjects with normal renal function and non-Japanese patients with renal impairment to evaluate the effects of renal impairment on the PK, PD effects, and safety of multiple oral doses of febuxostat.

Subjects received febuxostat 80 mg qd before breakfast for 7 days.

All 32 treated subjects were included in safety analysis, and of these, 31 subjects (11 with normal renal function, 6 with mild renal impairment, 7 with moderate renal impairment, 7 with severe renal impairment)[28] were included in PK analysis. Excluded was 1 patient with severe renal impairment who withdrew from the study due to personal reasons. Of these, 29 subjects were included in PD analysis. Excluded were 1 patient with moderate renal impairment and 1 patient with severe renal impairment from whom samples scheduled to be collected on the previous day of treatment were actually collected after the first dose.

The ratios of mean plasma PK parameters and urinary excretion rate of unchanged febuxostat in patients with mild, moderate, and severe renal impairment, respectively, to the corresponding parameters in subjects with normal renal function on Day 7 were as follows: t_{max}, 1.2, 0.8, and 0.8; C_{max}, 1.4, 1.0, and 1.0; $C_{max,\,u}$, 1.4, 1.0, and 1.3; $AUC_{0\text{-}24h}$, 1.5, 1.5, and 1.8; $AUC_{0\text{-}24h,\,u}$, 1.5, 1.4, and 2.3; and $t_{1/2}$, 1.6, 1.9, and 1.5; and the mean urinary excretion rate within 24 hours post-dose, 1.0, 0.8, and 0.5.

The ratios of mean PD parameters in patients with mild, moderate, and severe renal impairment, respectively, to the corresponding parameters in subjects with normal renal function on Day 7 were as follows: rate of change in $C_{mean,\,24h}$ of serum urate, 1.1, 1.0, and 0.9; $C_{mean,\,24h}$ of serum xanthine, 1.4, 2.6, and 4.2; 24-hour urinary urate excretion, 0.5, 0.3, and 0.5; 24-hour urinary xanthine excretion, 0.9, 0.8, and 0.5; and 24-hour urinary hypoxanthine excretion, 0.8, 0.4, and 0.1.

Adverse events were reported by 6, 3, 4 and 7 subjects, respectively, with normal renal function, mild, moderate, or severe renal impairment; and adverse drug reactions by 4, 1, 3, and 2 subjects, respectively. All events were mild in severity except for the moderate hypertension and acidosis (1 event each) reported by patients with severe renal impairment and moderate constipation (1 event) reported by 1 patient with mild renal impairment.

(d) Study of safety, PK, and PD effects in patients with hepatic impairment (5.3.3.3-5, Study TMX-[redacted]-012 [[redacted] 20[redacted] to [redacted] 20[redacted]], Reference data)

An open-label, parallel-group comparative study was conducted to compare the safety, PK, and PD effects of febuxostat in non-Japanese patients with hepatic impairment to those in subjects with normal hepatic function.

Subjects received febuxostat 80 mg qd before breakfast for 7 days.

All 28 treated subjects were included in safety analysis, and of these, 27 subjects (11 with normal hepatic function, 8 with mild hepatic impairment, 8 with moderate hepatic impairment)[29] were included in PK and PD analyses. Excluded was 1 subject with normal hepatic function who may have missed doses of febuxostat during the study period.

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[28] Classified into the following 4 groups according to 24-hour C_{CR} measured on the day before the start of treatment: subjects with normal renal function, C_{CR} >80 mL/min; patients with mild renal impairment, C_{CR} ≥50 to 80 mL/min; patients with moderate renal impairment, C_{CR} ≥30 to 49 mL/min; patients with severe renal impairment, C_{CR} ≥10 to 29 mL/min).

[29] Classified according to Child-Pugh classification (patients with mild hepatic impairment, Child-Pugh A; and patients with moderate hepatic impairment, Child-Pugh B)

The ratios of mean plasma PK parameters of unchanged febuxostat in patients with mild and moderate hepatic impairment to those in subjects with normal hepatic function on Day 7 was as follows: t_{max}, 1.0 and 0.6; C_{max}, 1.2 and 1.5; $C_{max,\ u}$, 1.2 and 1.2; $AUC_{0\text{-}24h}$, 1.3 and 1.5; $AUC_{0\text{-}24h,u}$, 1.3 and 1.2; and $t_{1/2}$, 1.3 and 1.0. The ratio of the mean urinary excretion rate within 24 hours post-dose was 1.3 and 1.4, respectively, for unchanged febuxostat.

The ratios of mean PD parameters in patients with mild and moderate hepatic impairment, respectively, to the corresponding PD parameters in subjects with normal hepatic function on Day 7 were as follows: the rate of change in $C_{mean,\ 24h}$ of serum urate, 0.8 and 0.8; $C_{mean,\ 24h}$ of serum xanthine, 1.1 and 1.0; 24-hour urinary urate excretion, 1.0 and 1.3; 24-hour urinary xanthine excretion, 0.7 and 0.7; and 24-hour urinary hypoxanthine excretion, 0.9 and 0.7.

Adverse events were reported by 3, 5, and 6 subjects, respectively, with normal hepatic function, mild, or moderate hepatic impairment; and adverse drug reactions by 2, 5, and 5 subjects, respectively. All these events were mild in severity.

(e) Study of effects of age and sex (5.3.3.3-1, Study TMX-[redacted]-016 [[redacted] 20[redacted]], Reference data)
An open-label, parallel-group comparative study was conducted in non-Japanese healthy adult subjects (target sample size, 24/sex) to evaluate the effects of age and sex on the safety, PK, and PD effects of multiple oral doses of febuxostat.

Subjects received febuxostat 80 mg qd before breakfast for 7 days.

All 48 treated subjects (24 young [18 to 40 years] and 24 elderly [≥65 years] subjects; 24/sex) were included in PK, PD, and safety analyses.

PK analysis showed that the ratios (elderly/young) of mean $C_{max,\ u}$, $AUC_{0\text{-}24h,\ u}$, and $t_{1/2}$ of plasma unchanged febuxostat on Day 7 were 1.0, 1.1, and 1.2, respectively, and the ratios (women/men) of those parameters of plasma unchanged febuxostat were 1.3, 1.2, and 1.0, respectively, and that the ratio (elderly/young) of the mean urinary excretion rate within 24 hours post-dose was 0.9 for unchanged febuxostat, and the ratio (women/men) of that mean urinary excretion rate was 1.1 for unchanged febuxostat.

The ratios (elderly/young and women/men, respectively) of mean PD parameters and 24-hour urinary excretion on Day 7 were as follows: the rate of change in $C_{mean,\ 24h}$ of serum urate, 1.0 and 1.1; $C_{mean,\ 24h}$ of serum xanthine, 1.2 and 0.8; urinary urate excretion, 0.8 and 0.6; urinary xanthine excretion, 1.1 and 1.0; and urinary hypoxanthine excretion, 0.9 and 0.8.

Adverse events and adverse drug reactions, respectively, were reported by 7 and 6 young subjects, 14 and 10 elderly subjects, 6 and 3 male subjects, and 15 and 13 female subjects. Adverse events reported more frequently by elderly subjects than by young subjects included constipation (3 young subjects, 7 elderly subjects) and trauma (0 young subjects, 2 elderly subjects). Adverse events reported more frequently by female subjects than by male subjects included constipation (1 male subject, 9 female subjects) and headache (0 male subjects, 3 female subjects).

4.(ii).A.(2).4) Drug interactions

(a) Study of effects of colchicine on PK of febuxostat (5.3.3.4-3, Study TMX-[redacted]-006 [[redacted] 20[redacted]], Reference data)
A randomized, open-label, two-period crossover study was conducted in non-Japanese healthy subjects (target sample size, 24 subjects) to evaluate the effects of colchicine on the PK of febuxostat.

In Period 1 and 2, subjects received febuxostat 40 mg qd before breakfast for 7 days (on Days 1-7) and colchicine 0.6 mg bid before breakfast and after the evening meal for 4 days (on Days 4-7) in combination (febuxostat + colchicine), or received febuxostat 40 mg qd alone before breakfast for 7 days (on Days 1-7).

All 22 treated subjects were included in PK and safety analyses.

PK analysis showed that the geometric mean ratios (febuxostat + colchicine/febuxostat alone) [two-sided 90% CI] of plasma C_{max} and $AUC_{0\text{-}24h}$ of unchanged febuxostat on Day 7 were 1.120 [0.980, 1.281] and 1.070 [1.025, 1.117], respectively.

Adverse events were reported by 6 subjects in combination therapy period and 5 subjects in monotherapy period.

(b) Study of effects of febuxostat on PK of colchicine (5.3.3.4-4, Study C[redacted]-006 [[redacted] to [redacted] 20[redacted]], Reference data)

A randomized, double-blind,[30] three-period crossover study was conducted in non-Japanese healthy subjects (target sample size, 33 subjects) to evaluate the effect of steady-state febuxostat on the PK of colchicine.

In Period 1, 2, and 3, subjects received febuxostat 120 mg qd and colchicine 0.6 mg bid in combination (febuxostat + colchicine), placebo qd and colchicine 0.6 mg bid (colchicine alone), or placebo qd and febuxostat 120 mg qd (febuxostat alone). Febuxostat and placebo were administered before breakfast, and colchicine before breakfast and after the evening meal, for 14 days.

All 33 treated subjects were included in safety analysis, and of these, 26 subjects were included in PK analysis. Excluded were 6 subjects who did not complete either of the 2 colchicine regimens (4 subjects due to adverse events, 2 subjects due to personal reasons) and 1 subject who may have missed doses of the study drug during Period 3 (combination therapy period).

PK analysis showed that the geometric mean ratios (febuxostat + colchicine/colchicine alone) [two-sided 90% CI] of plasma C_{max}, $AUC_{0\text{-}12h}$, and $AUC_{0\text{-}24h}$ of colchicine after the morning dose on Day 14 (1 subject was excluded from the analysis because of abnormal plasma colchicine levels at 24 hours post-dose) were 0.885 [0.813, 0.963], 0.963 [0.912, 1.017], and 0.974 [0.927, 1.024], respectively.

Adverse events were reported by 25 subjects in combination therapy period, 16 subjects in colchicine monotherapy period, and 19 subjects in febuxostat monotherapy period. A total of 5 subjects were withdrawn from the study due to adverse events (pancreatitis on Day 7 in febuxostat monotherapy period, serum AST increased/CK increased on Day 7 in combination therapy period, hepatitis on Day 10 in combination therapy period, anaemia/hypochromic anaemia on Day 28 in colchicine monotherapy period, iron deficiency anaemia on Day 47 in colchicine monotherapy period); the events of pancreatitis and CK increased were severe, and all events were considered to be adverse drug reactions except for the event of iron deficiency anaemia.

(c) Drug interaction study with naproxen (5.3.3.4-2, Study C[redacted]-013 [[redacted] to [redacted] 20[redacted]], Reference data)

A randomized, open-label, three-period crossover study was conducted in non-Japanese healthy subjects (target sample size, 27 subjects) to evaluate drug-drug interactions of concomitant use of febuxostat with naproxen.

In Period 1, 2, and 3, subjects received febuxostat 80 mg qd, naproxen 500 mg bid, or febuxostat 80 mg qd and naproxen 500 mg bid in combination (febuxostat + naproxen). Febuxostat was administered after breakfast, and naproxen after morning and evening meals, for 7 days.

All 27 treated subjects were included in safety analysis, and of these, 25 subjects were included in PK analysis.[31] Excluded were 2 subjects who did not complete the 2 febuxostat regimens or 2 naproxen regimens (due to adverse events)

PK analysis showed that the geometric mean ratios (febuxostat + naproxen/febuxostat alone) [two-sided 90% CI] of plasma C_{max} and $AUC_{0\text{-}24h}$ of unchanged febuxostat on Day 7 were 1.280 [1.1812, 1.3874]

[30] Colchicine was administered in an unblinded fashion.
[31] A total of 25 and 24 subjects completed the 2 febuxostat and 2 naproxen regimens, respectively, and were included in the respective analysis.

and 1.396 [1.3325, 1.4621], respectively, and that the geometric mean ratios (febuxostat + naproxen/naproxen alone) [two-sided 90% CI] of plasma C_{max}, $AUC_{0\text{-}12h}$, and $AUC_{0\text{-}24h}$ of naproxen after the morning dose on Day 7 were 1.001 [0.9753, 1.0272], 1.013 [0.9927, 1.0332], and 0.996 [0.9801, 1.0127], respectively.

Adverse events were reported by 9 subjects in febuxostat monotherapy period, 9 subjects in naproxen monotherapy period, and 9 subjects in combination therapy period. A total of 3 subjects were withdrawn from the study due to an adverse event (moderate cough, mild liver function test abnormal, and moderate angioedema occurred in 1 subject each, respectively, on Days 1, 4, and 5 in naproxen monotherapy period).

(d) Drug interaction study with indomethacin (5.3.3.4-6, Study TMX-[redacted]-017 [redacted] to [redacted] 20[redacted], Reference data)

A randomized, open-label, three-period crossover study was conducted in non-Japanese healthy subjects (target sample size, 27 subjects) to evaluate drug-drug interactions of concomitant use of febuxostat with indomethacin.

In Period 1, 2, and 3, subjects received febuxostat 80 mg qd, indomethacin 50 mg bid, or febuxostat 80 mg qd and indomethacin 50 mg bid in combination (febuxostat + indomethacin). Febuxostat was administered after breakfast, and indomethacin after morning and evening meals, for 5 days.

All 27 treated subjects were included in safety analysis, and of these, 26 subjects were included in PK analysis. Excluded was 1 subject who did not complete the combination regimen (withdrawn due to an adverse event)

PK analysis showed that the geometric mean ratios (febuxostat + indomethacin/febuxostat alone) [two-sided 90% CI] of plasma C_{max} and $AUC_{0\text{-}24h}$ of unchanged febuxostat on Day 5 were 0.931 [0.8189, 1.0579] and 1.017 [0.9739, 1.0610], respectively, and that the geometric mean ratios (febuxostat + indomethacin/indomethacin alone) [two-sided 90% CI] of plasma C_{max}, $AUC_{0\text{-}12h}$, and $AUC_{0\text{-}24h}$ of indomethacin after the morning dose on Day 5 were 0.981 [0.9117, 1.0564], 1.070 [1.0405, 1.1011], and 0.997 [0.9629, 1.0322], respectively.

Adverse events were reported by 10 subjects in febuxostat monotherapy period, 14 subjects in indomethacin monotherapy period, and 17 subjects in combination therapy period. One subject was withdrawn from the study after completion of combination therapy due to moderate dermatitis contact.

(e) Drug interaction study with theophylline (5.3.3.4-10, Study TMX-67_101 [redacted] to [redacted] 20[redacted], Reference data)

A randomized, double-blind, two-period crossover study was conducted in non-Japanese healthy subjects (target sample size, 24 subjects) to evaluate the effect of steady-state febuxostat on the PK of theophylline.

In Period 1 and 2, subjects received placebo or febuxostat 80 mg qd before breakfast for 7 days (on Days 1-7), in combination with a single oral dose of anhydrous theophylline 400 mg in the morning on Day 5 under fasted conditions.

All 24 treated subjects were included in PK[32] and safety analyses.

PK analysis showed that the geometric mean ratios ([theophylline + febuxostat]/[theophylline + placebo]) [two-sided 90% CI] of plasma C_{max} and $AUC_{0\text{-}t}$ of theophylline on Day 5 were 1.03 [0.917, 1.149] and 1.04 [0.927, 1.156], respectively. The trough levels (mean ± SD[33]) of unchanged febuxostat on Days 5 and 6 were 28.1 ± 10.8 ng/mL and 32.6 ± 13.3 ng/mL, respectively. In subjects receiving theophylline + placebo therapy and theophylline + febuxostat therapy, the urinary excretion within 72 hours post-dose on Day 5 was 56.2 ± 17.4 mg and 3.1 ± 4.0 mg, respectively, of 1-methylurate; 0.1 ±

[32] Geometric mean ratios of C_{max} and $AUC_{0\text{-}t}$ were calculated from the data of 23 subjects who completed both periods (1 subject was withdrawn from the study before completing Period 2 [theophylline + placebo therapy] due to positive cotinine test).

[33] Calculated from the data of the same 23 subjects as in footnote 32

0.4 mg and 40.1 ± 7.6 mg, respectively, of 1-methylxanthine; 30.9 ± 11.6 mg and 26.9 ± 9.5 mg, respectively, of 3-methylxanthine; and 114.8 ± 32.2 mg and 105.2 ± 23.3 mg, respectively, of 1,3-dimethylurate.

Seven adverse events were reported by 3 subjects in theophylline + febuxostat therapy period and 5 adverse events by 3 subjects in theophylline + placebo therapy period.

(f) Other drug interaction studies (5.3.3.4-1, 5.3.3.4-5, and 5.3.3.4-7 to 5.3.3.4-9; Studies C[redacted]-005, TMX-[redacted]-014, C03-059, C03-057, and F-P[redacted]-162 [[redacted] 20[redacted] to [redacted] 20[redacted]], Reference data)

The results of drug interaction studies conducted in non-Japanese healthy subjects are shown in Table 7.

Table 7. Results of other drug interaction studies

Study Identifier	Dose of febuxostat	Tested drug and its dose	Analyte in plasma (n)	C_{max} ratio[a)] [90% CI]	AUC[b)] ratio[a)] [90% CI]
C[redacted]-005	120 mg/dose	Desipramine 25 mg/dose	Desipramine (n = 18)	1.163 [1.0967, 1.2324]	1.242 [1.1369, 1.3570]
			2-Hydroxydesipramine (n = 18)	0.959 [0.9026, 1.0183]	1.059 [1.0089, 1.1122]
TMX-[redacted]-014	80 mg/dose	Liquid antacid[c)] 20 mL/dose	Unchanged febuxostat (n = 24)	0.676 [0.581, 0.786]	0.849 [0.802, 0.899]
C03-059	80 mg/dose	Hydrochlorothiazide 50 mg/dose	Unchanged febuxostat (n = 33)	1.001 [0.8593, 1.1664]	1.033 [0.9758, 1.0943]
C03-057	120 mg/dose	Warfarin[d)]	(*R*)-Warfarin (n = 13)	1.008 [0.9320, 1.0909]	1.022 [0.9792, 1.0670]
			(*S*)-Warfarin (n = 13)	1.011 [0.9073, 1.1261]	1.048 [1.0053, 1.0928]
F-P[redacted]-162	80 mg/dose	Warfarin[e)]	(*R*)-Warfarin (n = 27)	0.9791 [0.9407, 1.0191]	0.9923 [0.9722, 1.0128]
			(*S*)-Warfarin (n = 27)	0.9973 [0.9534, 1.0432]	1.0103 [0.9887, 1.0323]

CI = confidence interval (two-sided)
a) Geometric mean ratio
b) $AUC_{0\text{-}t}$ is presented for Studies C[redacted]-005, TMX-[redacted]-014, C03-059, and F-P[redacted]-162, and $AUC_{0\text{-}24h}$ is presented for Study C03-057.
c) Contains 200 mg of magnesium hydroxide and 225 mg of aluminum hydroxide in 5 mL of solution.
d) The dose was selected to maintain INR values between 1.2 and 1.8.
e) The dose was selected to maintain INR values between 1.5 and 2.0.

4.(ii).B Outline of the review by PMDA

4.(ii).B.(1) PK and PD effects in patients with renal impairment

PMDA asked the applicant to explain the PK and PD effects in patients with renal impairment receiving febuxostat 60 mg at unspecified times of day.

The applicant's response:

By considering the food effect observed in patients with mild or moderate renal impairment in Study TMX-67-[redacted] and assuming linearity, C_{max} and $AUC_{0\text{-}24h}$ in those patients following 7-day treatment with febuxostat 60 mg qd under fasted conditions were estimated to be 2100.25 ng/mL and 11,846.65 ng·h/mL, respectively, in patients with mild renal impairment, and 2590.89 ng/mL and 13,016.35 ng·h/mL, respectively, in patients with moderate renal impairment, based on the data from Study TMX-67-[redacted]. The respective PK parameters in patients with severe renal impairment were estimated to be 2841 ng/mL and 16,656 ng·h/mL based on the following: (i) C_{max} (1967 ng/mL) and $AUC_{0\text{-}24h}$ (7760 ng·h/mL) following multiple doses of febuxostat 60 mg after a meal were estimated from mean exposures in subjects receiving febuxostat 40 and 80 mg in Study TMX-67-[redacted]; (ii) the mean C_{max} and $AUC_{0\text{-}24h}$ in patients with severe renal impairment in Study TMX-[redacted]-008 were 1.04- and 1.76-fold higher than those in subjects with normal renal function; and (iii) the effect of food in Study TMX-67-[redacted]. Consequently, the estimated exposure in patients with renal impairment receiving febuxostat 60 mg under fasted conditions did not exceed the exposure (C_{max}, 5085.12 ng/mL; $AUC_{0\text{-}24h}$, 23,061.50 ng·h/mL) found tolerable in healthy adult subjects receiving febuxostat 160 mg. The rate of change in $C_{mean,\ 24h}$ of plasma urate in patients with renal impairment receiving febuxostat 60 mg at unspecified times of day was estimated to be comparable to that (-59.9%) in subjects with normal renal function irrespective of the timing of meals or of the level of renal function based on the following findings: (i) the rate of change in blood urate from baseline was largely consistent irrespective of the severity of renal

impairment in Studies TMX-67-[redacted] and TMX-[redacted]-008; (ii) $C_{mean, 48h}$ of plasma urate in Study TMX-67-[redacted] was largely consistent irrespective of meal conditions; and (iii) the rate of change in $C_{mean, 24h}$ of plasma urate in subjects with normal renal function receiving febuxostat 60 mg was estimated to be -59.9% based on the data from Study TMX-67-[redacted] assuming the dose-proportionality in the dose range of 40 to 80 mg of febuxostat. On the assumption of the same dose proportionality, $C_{mean, 24h}$ of plasma xanthine in subjects with normal renal function receiving febuxostat 60 mg was estimated to be 0.150 mg/dL based on the data from Study TMX-67-[redacted]. There was no difference in $C_{mean, 48h}$ of plasma xanthine between the postprandial and fasted groups in Study TMX-67-[redacted], and also, the ratio (patients with severe renal impairment/subjects with normal renal function) of $C_{mean, 24h}$ of plasma xanthine was expected to be similar between Japanese and non-Japanese subjects because ratios of $C_{mean, 24h}$ of plasma xanthine for patients with mild and moderate renal impairment to those with severe renal impairment seen in Study TMX-67-[redacted] (1.78 and 2.11, respectively) were comparable to the ratios in Study TMX-[redacted]-008 (1.42 and 2.55, respectively). Therefore, $C_{mean, 24h}$ of plasma xanthine in subjects with renal impairment receiving febuxostat 60 mg at unspecified times of day was estimated to be 0.27 mg/dL in patients with mild renal impairment, 0.32 mg/dL in patients with moderate renal impairment, and 0.63 mg/dL in patients with severe renal impairment, which were comparable to or lower than that (0.6293 mg/dL) in non-Japanese patients with severe renal impairment receiving febuxostat 80 mg.

PMDA's view on the use in patients with renal impairment from the perspective of PK and PD effects:
The applicant discussed the PK in patients with renal impairment only from the viewpoint of total (bound + unbound febuxostat) exposure. However, in Studies TMX-67-[redacted] and TMX-[redacted]-008, the increase in exposure to unbound febuxostat was greater than the increase in total (bound + unbound febuxostat) exposure, and blood xanthine levels were increased with decreasing renal function although no rapid fall in blood urate was observed, and therefore, careful administration is needed. In light of the above, use in patients with renal impairment will be additionally reviewed in terms of efficacy and safety [see "4.(iii).B.(6).1) Patients with renal impairment"].

4.(ii).B.(2) Drug interactions

PMDA asked the applicant to explain the interactions of febuxostat with azathioprine and 6-mercaptopurine and the need to contraindicate concomitant use of febuxostat with these drugs also in Japan in light of the following facts: when in combination with allopurinol, azathioprine and 6-mercaptopurine, which are metabolized by XOD, have been required to be carefully administered and also, when in combination with febuxostat, may increase blood 6-mercaptopurine levels through XOD inhibition leading to an increased risk of adverse drug reactions including bone marrow depression; febuxostat in *in vitro* showed an approximately 200- to 1200-fold stronger inhibition of XOD than allopurinol according to the applicant's explanation (Osada Y, et al., *Eur J Pharmacol*. 1993;241:183-188); and co-administration of febuxostat with azathioprine or 6-mercaptopurine is contraindicated in the US labeling of febuxostat.

The applicant's response:
At the time of regulatory submission to the US Food and Drug Administration (FDA), Takeda Pharmaceutical North America (TPNA) (formerly TAP Pharmaceutical Products Inc.) presented a warning statement regarding co-administration of febuxostat with azathioprine or 6-mercaptopurine, as is the case with the warning of allopurinol, but, on the basis of an opinion from FDA that such co-administration should be contraindicated if no clinical studies on drug interaction between febuxostat and these drugs were conducted, TPNA agreed to contraindicate such co-administration, expressing an opinion that such studies might pose a safety risk to the participants. However, such co-administration does not need to be contraindicated in Japan for the following reasons: although *in vitro* XOD inhibition by febuxostat was shown to be stronger than that by allopurinol, the levels of XOD inhibition in humans are also affected by PK of each drug; therefore, the relative levels of XOD inhibition between febuxostat and allopurinol should be evaluated based not only on the *in vitro* inhibition but also on the relative blood urate lowering activity in clinical studies. Pooled data from 5 Japanese clinical studies of febuxostat demonstrated that the blood urate lowering activity of febuxostat as measured by the rate of change in serum urate level (-41.9% and -49.2% at 40 and 60 mg [proposed doses], respectively) was 1.14 to 1.40 times that of allopurinol (-35.2% and -36.6% at 200 and 300 mg/day [usual doses], respectively). Precautionary statements are included in the package insert of allopurinol recommending that 1/3 to 1/4 times the usual dose of azathioprine or 6-mercaptopurine be administered concomitantly

to avoid an increased risk of adverse drug reactions including bone marrow depression resulting from elevated blood 6-mercaptopurine levels caused by inhibition of XOD, a metabolizing enzyme of azathioprine or 6-mercaptopurine, by allopurinol. Consequently, febuxostat + azathioprine or febuxostat + 6-mercaptopurine with approximately 1/3 to 1/6 times the usual dose azathioprine or 6-mercaptopurine would not lead to a higher blood azathioprine or 6-mercaptopurine level than that expected with allopurinol + azathioprine or allopurinol + 6-mercaptopurine with recommended dose (i.e., 1/3 to 1/4 times the usual dose), and thus, the risk of adverse drug reactions is unlikely to be increased as compared with combination therapy with allopurinol. Therefore, febuxostat + azathioprine or febuxostat + 6-mercaptopurine does not need to be contraindicated. In the European labeling of febuxostat, febuxostat + azathioprine or febuxostat + 6-mercaptopurine is not contraindicated but listed in the Precautions for Co-administration section.

PMDA asked the applicant to explain the interactions of febuxostat with cyclophosphamide and ifosfamide, for which careful administration is required when used concomitantly with allopurinol, as well as with vidarabine (intravenous infusion) and didanosine, which are metabolized by XOD.

The applicant's response:
Patients receiving cyclophosphamide or ifosfamide in combination with allopurinol have elevated blood levels of cyclophosphamide or ifosfamide and experience bone marrow depression more frequently than those receiving cyclophosphamide or ifosfamide monotherapy (Endoxan Tablets 50 mg [interview form], Ifomide for Injection 1 g [interview form]). However, their detailed mechanism is unclear, and no reports show the involvement of XOD inhibition by allopurinol. Therefore, febuxostat is unlikely to cause significant adverse drug reactions induced by XOD inhibition-based interactions when it is used with cyclophosphamide or ifosfamide. In the Japanese clinical studies, 1 subject received febuxostat 5 mg qd concomitantly with 750 mg of cyclophosphamide (a single intravenous injection), and no adverse events were reported. Consequently, at present, there is no need to provide a precautionary statement regarding concomitant use of febuxostat with cyclophosphamide or ifosfamide. A precautionary statement is included in the draft package insert, as with allopurinol, that febuxostat, when in combination with vidarabine (intravenous infusion) or didanosine, should be carefully administered because XOD inhibition-based drug-drug interactions cannot be ruled out as is the case with allopurinol.

PMDA's view:
The applicant's response regarding vidarabine (intravenous infusion) and didanosine is acceptable. The applicant's response regarding cyclophosphamide and ifosfamide is acceptable at present, however, given that it is unclear whether the mechanism of interactions with allopurinol is associated with XOD inhibition, new findings, if available, should be appropriately provided to healthcare professionals. Meanwhile, because it cannot be concluded yet whether the safety of febuxostat + azathioprine or 6-mercaptopurine combination is ensured even with azathioprine or 6-mercaptopurine co-administered at an approximately 1/3 to 1/6 usual dose, such combination treatment should be contraindicated at present. The above points will be finalized, taking account of comments raised in the Expert Discussion.

4.(iii) Summary of clinical efficacy and safety

4.(iii).A Summary of the submitted data

The applicant submitted evaluation data, namely the results from Japanese phase II studies (Studies TMX-67-[redacted], TMX-67-[redacted], and TMX-67-[redacted]), phase III studies (Studies TMX-67-[redacted] and TMX-67-[redacted]), and long-term treatment studies (Studies TMX-67-[redacted] and TMX-67-[redacted]). In addition, the applicant submitted reference data, namely the results from foreign clinical studies (Studies F-GT06-153, C[redacted]-009, C[redacted]-010, TMX-67_III_20[redacted], TMX-[redacted]-005, and C02-021). Primary study results are shown below. Because some Japanese studies were completed ≥10 years earlier, the applicant examined the storage status of source documents at all study sites prior to submitting the application. As a result, 53 subjects were identified as not linked to their medical records or informed consent forms (9 subjects in Study TMX-67-[redacted], 31 subjects in Study TMX-67-[redacted], 12 subjects in Study TMX-67-[redacted], 1 subject in Study TMX-67-[redacted]). During the current review, PMDA confirmed both study results obtained from data including and excluding, and has concluded that there is no particular problem with describing study results excluding these subjects in this Review Report.

4.(iii).A.(1) Japanese phase II studies

4.(iii).A.(1).1) Placebo-controlled dose-response study (5.3.5.1-1, Study TMX-67-[redacted] [redacted] to [redacted] 20[redacted])

A randomized, double-blind, placebo-controlled, parallel-group comparative study was conducted to evaluate the dose response relationship, efficacy, and safety of febuxostat in patients with hyperuricemia including gout[34] (target sample size, 120 subjects [30/group]).

Subjects received orally placebo or febuxostat 10, 20, or 40 mg qd after breakfast. Subjects in the febuxostat group received orally febuxostat 10 mg for the first 2 weeks, and then febuxostat 10, 20, or 40 mg qd. The duration of treatment was 8 weeks.

All 117 treated subjects (28 in the placebo group, 29 in the 10 mg group, 29 in the 20 mg group, 31 in the 40 mg group) were included in the full analysis set (FAS), in which primary efficacy and safety were assessed. A total of 2 subjects discontinued the study; the reasons included an adverse event (in the febuxostat 40 mg group) and personal reasons (in the febuxostat 10 mg group).

The rate of change in serum urate level from baseline to Week 8, the primary efficacy endpoint, is shown in Table 8. There was a significant difference between each febuxostat group and the placebo group.

Table 8. Rate of change in serum urate level from baseline to Week 8 (FAS)

Treatment group (number of subjects analyzed)	Serum urate level		Adjusted *P* value[a)]
	Baseline (mg/dL)	Rate of change (%)	
Placebo (N = 28)	8.82 ± 1.01	-0.3 ± 10.6	-
Febuxostat 10 mg (N = 29)	9.21 ± 1.38	-23.9 ± 11.2	$P < 0.001$
Febuxostat 20 mg (N = 29)	8.97 ± 1.26	-33.5 ± 13.2	$P < 0.001$
Febuxostat 40 mg (N = 31)	8.97 ± 1.14	-43.1 ± 8.4	$P < 0.001$

Mean ± SD; last observation carried forward (LOCF)

a) Dunnett-Hsu multiple comparison[35] with baseline serum urate level and study site as covariates with a one-sided significance level of 2.5%

The percentage of subjects who achieved serum urate levels ≤6.0 mg/dL at Week 8, the secondary endpoint, is shown in Table 9.

Table 9. Percentage of subjects who achieved serum urate levels of ≤6.0 mg/dL at Week 8 (FAS)

Treatment group (number of subjects analyzed)	Percentage of subjects who achieved serum urate levels of ≤6.0 mg/dL
Placebo (N = 28)	0.0 (0/28)
Febuxostat 10 mg (N = 29)	24.1 (7/29)
Febuxostat 20 mg (N = 29)	65.5 (19/29)
Febuxostat 40 mg (N = 31)	77.4 (24/31)

Achievement rate (%) (number of subjects who achieved the serum urate levels/number of subjects analyzed)

Adverse events (including abnormal changes in laboratory values) were reported by 22 of 28 subjects (78.6%, 50 events) in the placebo group, 19 of 29 subjects (65.5%, 62 events) in the febuxostat 10 mg group, 22 of 29 subjects (75.9%, 71 events) in the 20 mg group, and 24 of 31 subjects (77.4%, 66 events) in the 40 mg group. Adverse events reported by ≥2 subjects in any group are shown in Table 10.

[34] Key inclusion criteria: patients with serum urate levels ≥8.0 mg/dL. Key exclusion criteria: patients with gouty arthritis or whose gouty arthritis has resolved for <2 weeks at enrollment; patients who had received prohibited drugs including gout suppressants and antihyperuricemics within 2 weeks prior to study treatment; patients with renal impairment (serum creatinine ≥1.5 mg/dL); patients with hepatic impairment (AST or ALT levels >2 times their local upper limit of normal).

[35] Hsu JC, *Journal of Computational Statistics and Graphics.* 1992;1:151-168.

Table 10. Adverse events reported by ≥2 subjects in any group

Adverse event	Placebo (N = 28)	Febuxostat 10 mg (N = 29)	Febuxostat 20 mg (N = 29)	Febuxostat 40 mg (N = 31)
Nasopharyngitis	3 (10.7)	5 (17.2)	1 (3.4)	5 (16.1)
Somnolence	0 (0.0)	1 (3.4)	2 (6.9)	0 (0.0)
Abdominal pain upper	2 (7.1)	1 (3.4)	0 (0.0)	0 (0.0)
Diarrhoea	2 (7.1)	1 (3.4)	1 (3.4)	2 (6.5)
Gouty arthritis	1 (3.6)	5 (17.2)	6 (20.7)	7 (22.6)
Thirst	0 (0.0)	0 (0.0)	2 (6.9)	0 (0.0)
ALT increased	2 (7.1)	2 (6.9)	4 (13.8)	2 (6.5)
AST increased	2 (7.1)	1 (3.4)	2 (6.9)	0 (0.0)
Urinary β_2-MG increased	3 (10.7)	1 (3.4)	6 (20.7)	2 (6.5)
NAG increased	4 (14.3)	3 (10.3)	4 (13.8)	4 (12.9)
Blood bilirubin increased	3 (10.7)	0 (0.0)	0 (0.0)	1 (3.2)
Blood CK increased	3 (10.7)	2 (6.9)	5 (17.2)	4 (12.9)
Blood triglycerides increased	4 (14.3)	1 (3.4)	5 (17.2)	2 (6.5)
C-reactive protein increased	1 (3.6)	8 (27.6)	2 (6.9)	9 (29.0)
γ-GTP increased	1 (3.6)	1 (3.4)	4 (13.8)	2 (6.5)
White blood cell count increased	0 (0.0)	3 (10.3)	2 (6.9)	2 (6.5)
Lymphocyte percentage decreased	0 (0.0)	2 (6.9)	0 (0.0)	0 (0.0)

Number of subjects who experienced the event (incidence, %); MedDRA/J Ver.12.0

Adverse drug reactions (including abnormal changes in laboratory values) were reported by 2 of 28 subjects (7.1%, 3 events) in the placebo group, 8 of 29 subjects (27.6%, 9 events) in the febuxostat 10 mg group, 5 of 29 subjects (17.2%, 7 events) in the 20 mg group, and 5 of 31 subjects (16.1%, 8 events) in the 40 mg group.

No deaths or serious adverse events were reported. Adverse events leading to study discontinuation included ALT increased and γ-GTP increased (1 event each) reported by 1 subject in the febuxostat 40 mg group, both of which resolved without intervention.

Gouty arthritis was reported by 1 of 28 subjects (3.6%, 1 event) in the placebo group, 5 of 29 subjects (17.2%, 5 events) in the febuxostat 10 mg group, 6 of 29 subjects (20.7%, 9 events) in the 20 mg group, and 7 of 31 subjects (22.6%, 14 events) in the 40 mg group.

4.(iii).A.(1).2) Placebo-controlled dose-response study (additional study) (5.3.5.1-2, Study TMX-67-[redacted] [[redacted] to [redacted] 20[redacted]])

A randomized, double-blind, placebo-controlled, parallel-group comparative study was conducted to evaluate the dose response relationship, efficacy, and safety of febuxostat in patients with hyperuricemia including gout[36] (target sample size, 200 subjects [40/group]).

Subjects received orally placebo or febuxostat 20, 40, 60, or 80 mg qd after breakfast. Febuxostat 10 mg was first administered, and the dose was subsequently increased in a stepwise manner to the fixed maintenance doses (20, 40, 60, or 80 mg qd) in the febuxostat groups (to 20 mg after 2 weeks of treatment, 40 mg after 6 weeks of treatment and 60 or 80 mg after 10 weeks of treatment). The duration of treatment was 16 weeks.

Among all 202 treated subjects, 199 subjects (38 in the placebo group, 43 in the febuxostat 20 mg group, 41 in the 40 mg group, 36 in the 60 mg group, 41 in the 80 mg group) were included in the FAS, in which primary efficacy and safety were assessed. Excluded were 3 subjects with deviations from procedure for collection of patient characteristics at enrollment. A total of 18 subjects discontinued the study; the reasons included an adverse event in 5 subjects (1 in the placebo group, 2 in the febuxostat 20 mg group, 1 in the 60 mg group, 1 in the 80 mg group), personal reasons in 3 subjects (1 each in the febuxostat 20, 40, and 60 mg groups), subject's request in 9 subjects (1 in the placebo group, 2 in the

[36] Key inclusion criteria: patients with gout (who had experienced ≥1 episode of gouty arthritis) with serum urate levels >7.0 mg/dL; patients with hyperuricemia who have a complication(s) (urinary calculus, hypertension, hyperlipemia, or impaired glucose tolerance requiring medication or therapy) with serum urate levels ≥8.0 mg/dL; patients with hyperuricemia having no complications with serum urate levels ≥9.0 mg/dL. Key exclusion criteria: patients with gouty arthritis or whose gouty arthritis has resolved for <2 weeks at blood sampling for the examination before and at enrollment; patients who have received prohibited drugs including gout suppressants and antihyperuricemics within 2 weeks prior to blood sampling for pre-registration examination; patients with renal impairment (serum creatinine ≥1.5 mg/dL); patients with hepatic impairment (AST or ALT levels >2 times their local upper limit of normal).

febuxostat 20 mg group, 2 in the 40 mg group, 1 in the 60 mg group, 3 in the 80 mg group), and others in 1 subject (febuxostat 60 mg group).

The percentage of subjects who achieved serum urate levels ≤6.0 mg/dL at Week 16, the primary efficacy endpoint, is shown in Table 11. There was a significant difference between each febuxostat group and the placebo group.

Table 11. Percentage of subjects who achieved serum urate levels ≤6.0 mg/dL at Week 16 (FAS)

Treatment group (number of subjects analyzed)	Percentage of subjects who achieved serum urate levels ≤6.0 mg/dL	*P* value[a)]
Placebo (N = 38)	2.6 (1/38)	-
Febuxostat 20 mg (N = 43)	46.5 (20/43)	*P* < 0.001
Febuxostat 40 mg (N = 41)	82.9 (34/41)	*P* < 0.001
Febuxostat 60 mg (N = 36)	83.3 (30/36)	*P* < 0.001
Febuxostat 80 mg (N = 41)	87.8 (36/41)	*P* < 0.001

Achievement rate (%) (number of subjects who achieved the serum urate levels/number of subjects analyzed); LOCF

a) Cochran-Mantel-Haenszel test with clinical diagnosis[37] and baseline serum urate level[38] as stratification factors, adjusted for multiplicity using closed testing procedure, with a two-sided significance level of 5%

The rate of change in serum urate level from baseline to Week 16, the secondary endpoint, is shown in Table 12.

Table 12. Rate of change in serum urate level from baseline to Week 16 (FAS)

Treatment group (number of subjects analyzed)	Serum urate level	
	Baseline (mg/dL)	Rate of change (%)
Placebo (N = 38)	8.94 ± 0.99	-2.07 ± 12.60
Febuxostat 20 mg (N = 43)	8.80 ± 1.29	-29.65 ± 11.50
Febuxostat 40 mg (N = 41)	8.58 ± 1.09	-40.59 ± 15.78
Febuxostat 60 mg (N = 36)	8.58 ± 1.00	-48.35 ± 17.93
Febuxostat 80 mg (N = 41)	8.60 ± 1.32	-52.02 ± 17.49

Mean ± SD; LOCF

Adverse events (including abnormal changes in laboratory values) were reported by 22 of 38 subjects (57.9%, 47 events) in the placebo group, 27 of 43 subjects (62.8%, 63 events) in the febuxostat 20 mg group, 25 of 41 subjects (61.0%, 56 events) in the 40 mg group, 24 of 36 subjects (66.7%, 46 events) in the 60 mg group, and 25 of 41 subjects (61.0%, 56 events) in the 80 mg group. Adverse events reported by ≥2 subjects in any group are shown in Table 13.

[37] Gout or hyperuricemia

[38] Classified into <9.0 mg/dL, ≥9.0 to <10.0 mg/dL, and ≥10.0 mg/dL

Table 13. Adverse events reported by ≥2 subjects in any group

Adverse event	Placebo (N = 38)	Febuxostat 20 mg (N = 43)	Febuxostat 40 mg (N = 41)	Febuxostat 60 mg (N = 36)	Febuxostat 80 mg (N = 41)
Nasopharyngitis	8 (21.1)	9 (20.9)	8 (19.5)	3 (8.3)	4 (9.8)
Seasonal allergy	1 (2.6)	1 (2.3)	0 (0.0)	0 (0.0)	2 (4.9)
Headache	1 (2.6)	0 (0.0)	1 (2.4)	2 (5.6)	0 (0.0)
Hypertension	2 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Upper respiratory tract inflammation	0 (0.0)	2 (4.7)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhoea	3 (7.9)	2 (4.7)	1 (2.4)	1 (2.8)	1 (2.4)
Pruritus	1 (2.6)	0 (0.0)	0 (0.0)	2 (5.6)	0 (0.0)
Arthralgia	2 (5.3)	0 (0.0)	2 (4.9)	2 (5.6)	2 (4.9)
Back pain	1 (2.6)	0 (0.0)	0 (0.0)	3 (8.3)	2 (4.9)
Gouty arthritis	2 (5.3)	4 (9.3)	3 (7.3)	3 (8.3)	9 (22.0)
Pain in extremity	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.6)	2 (4.9)
Spinal osteoarthritis	2 (5.3)	1 (2.3)	0 (0.0)	1 (2.8)	0 (0.0)
Limb discomfort	2 (5.3)	1 (2.3)	1 (2.4)	0 (0.0)	2 (4.9)
Malaise	0 (0.0)	3 (7.0)	0 (0.0)	0 (0.0)	1 (2.4)
ALT increased	1 (2.6)	1 (2.3)	0 (0.0)	1 (2.8)	2 (4.9)
Urinary β_2-MG increased	0 (0.0)	2 (4.7)	1 (2.4)	1 (2.8)	0 (0.0)
Blood CK increased	0 (0.0)	1 (2.3)	1 (2.4)	0 (0.0)	3 (7.3)
Blood glucose increased	0 (0.0)	0 (0.0)	2 (4.9)	0 (0.0)	2 (4.9)
Blood TSH increased	0 (0.0)	1 (2.3)	2 (4.9)	0 (0.0)	0 (0.0)
Blood triglycerides increased	3 (7.9)	2 (4.7)	1 (2.4)	1 (2.8)	1 (2.4)
γ-GTP increased	0 (0.0)	2 (4.7)	1 (2.4)	1 (2.8)	1 (2.4)
Glucose urine present	0 (0.0)	0 (0.0)	2 (4.9)	0 (0.0)	0 (0.0)
Eosinophil percentage increased	0 (0.0)	0 (0.0)	2 (4.9)	0 (0.0)	0 (0.0)

Number of subjects who experienced the event (incidence, %); MedDRA/J Ver.12.0

Adverse drug reactions (including abnormal changes in laboratory values) were reported by 7 of 38 subjects (18.4%, 14 events) in the placebo group, 10 of 43 subjects (23.3%, 22 events) in the febuxostat 20 mg group, 12 of 41 subjects (29.3%, 19 events) in the 40 mg group, 5 of 36 subjects (13.9%, 8 events) in the 60 mg group, and 12 of 41 subjects (29.3%, 22 events) in the 80 mg group.

No deaths were reported. A total of 3 serious adverse events were reported by 3 subjects (1 event in 1 subject in the placebo group [nephrotic syndrome], 2 events in 2 subjects in the febuxostat 60 mg group [cerebral infarction, finger deformity]), for all of which a causal relationship to the study drug was ruled out. Four subjects discontinued the study due to non-serious adverse events including urticaria, ALT increased/AST increased/γ-GTP increased, and rash/hepatic function abnormal in 1 subject each in the febuxostat 20 mg group and hyperthyroidism in the 80 mg group.

Gouty arthritis was reported by 2 of 38 subjects (5.3%, 4 events) in the placebo group, 4 of 43 subjects (9.3%, 5 events) in the febuxostat 20 mg group, 3 of 41 subjects (7.3%, 4 events) in the 40 mg group, 3 of 36 subjects (8.3%, 6 events) in the 60 mg group, and 9 of 41 subjects (22.0%, 15 events) in the 80 mg group.

4.(iii).A.(1).3) Allopurinol-controlled exploratory study (additional study) (5.3.5.1-5, Study TMX-67-[redacted])

A randomized, open-label, allopurinol-controlled, parallel-group comparative study was conducted to evaluate the efficacy of allopurinol versus febuxostat in patients with hyperuricemia including gout[39] (target sample size, 40 subjects).

Febuxostat 10 mg qd was first administered, and the dose was subsequently increased in a stepwise manner to the fixed maintenance doses (40 or 60 mg qd) in the febuxostat groups (to 20 mg qd after 2 weeks of treatment, 40 mg qd after 6 weeks of treatment, and 60 mg qd after 10 weeks of treatment).

[39] Key inclusion criteria: patients with gout (who had experienced ≥1 episode of gouty arthritis) with serum urate levels >7.0 mg/dL; patients with hyperuricemia who have a complication(s) (urinary calculus, hypertension, hyperlipemia, or impaired glucose tolerance requiring medication or therapy) with serum urate levels ≥8.0 mg/dL; patients with hyperuricemia having no complications with serum urate levels ≥9.0 mg/dL. Key exclusion criteria: patients with gouty arthritis or whose gouty arthritis has resolved for <2 weeks at blood sampling for the examination before and at enrollment; patients who have received prohibited drugs including gout suppressants and antihyperuricemics within 2 weeks prior to blood sampling for pre-registration examination; patients with renal impairment (serum creatinine ≥1.5 mg/dL); patients with hepatic impairment (AST or ALT levels >2 times their local upper limit of normal).

Allopurinol 100 mg qd was first administered, and the dose was subsequently increased in a stepwise manner to the fixed maintenance dose (300 mg/day) (i.e., to 200 mg/day after 2 weeks, and to 300 mg/day after 6 weeks of treatment).

Febuxostat was administered once daily after breakfast throughout the treatment period, and allopurinol was first administered once daily after breakfast for the initial 2 weeks, then twice daily after morning and evening meals until 6 weeks into treatment, and at last thrice daily after each meal until 16 weeks into treatment. The duration of treatment was 16 weeks.

All 40 treated subjects (10 in the febuxostat 40 mg group, 10 in the 60 mg group, 20 in the allopurinol group) were included in safety analysis, and of these, 38 subjects were included in the FAS, in which primary efficacy was assessed. Excluded were 2 subjects (1 each in the febuxostat 60 mg and allopurinol groups) with no serum urate data after baseline. A total of 3 subjects discontinued the study; the reasons included personal reasons (in the febuxostat 60 mg group), subject's wish (in the 60 mg group), and worsening of complications (in the allopurinol group).

The rate of change in serum urate level from baseline to Week 16, the primary efficacy endpoint, is shown in Table 14.

Table 14. Rate of change in serum urate level from baseline to Week 16 (FAS)

Treatment group (number of subjects analyzed)	Serum urate level	
	Baseline (mg/dL)	Rate of change [95% CI]
Febuxostat 40 mg (N = 10)	8.64 ± 0.77	-42.96 ± 13.33 [-52.50, -33.42]
Febuxostat 60 mg (N = 9)	8.48 ± 1.15	-52.47 ± 9.79 [-60.00, -44.94]
Allopurinol (N = 19)	8.34 ± 1.16	-36.55 ± 18.59 [-45.52, -27.59]

Mean ± SD; LOCF

The percentage of subjects who achieved serum urate levels ≤6.0 mg/dL at Week 16 (LOCF), the secondary endpoint, was 90.0% (9 of 10 subjects) in the febuxostat 40 mg group, 88.9% (8 of 9 subjects) in the 60 mg group, and 73.7% (14 of 19 subjects) in the allopurinol group.

Adverse events (including abnormal changes in laboratory values) were reported by 8 of 10 subjects (80.0%, 25 events) in the febuxostat 40 mg group, 5 of 10 subjects (50.0%, 9 events) in the 60 mg group, and 16 of 20 subjects (80.0%, 39 events) in the allopurinol group. Adverse events reported by ≥2 subjects in any group are shown in Table 15.

Table 15. Adverse events reported by ≥2 subjects in any group

Adverse event	Febuxostat 40 mg (N = 10)	Febuxostat 60 mg (N = 10)	Allopurinol (N = 20)
Upper respiratory tract inflammation	2 (20.0)	0 (0.0)	1 (5.0)
Gouty arthritis	1 (10.0)	1 (10.0)	4 (20.0)
ALT increased	0 (0.0)	1 (10.0)	2 (10.0)
AST increased	0 (0.0)	0 (0.0)	2 (10.0)
Urinary β_2-MG increased	3 (30.0)	1 (10.0)	2 (10.0)
Blood CK increased	2 (20.0)	0 (0.0)	4 (20.0)
Blood triglycerides increased	3 (30.0)	0 (0.0)	1 (5.0)
C-reactive protein increased	1 (10.0)	0 (0.0)	3 (15.0)
γ-GTP increased	0 (0.0)	0 (0.0)	3 (15.0)

Number of subjects who experienced the event (incidence, %); MedDRA/J Ver.12.0

Adverse drug reactions (including abnormal changes in laboratory values) were reported by 6 of 10 subjects (60.0%, 8 events) in the febuxostat 40 mg group, 2 of 10 subjects (20.0%, 6 events) in the 60 mg group, and 5 of 20 subjects (25.0%, 9 events) in the allopurinol group.

No deaths, serious adverse events, or adverse events leading to study discontinuation were reported.

Gouty arthritis was reported by 1 of 10 subjects (10.0%, 1 event) in the febuxostat 40 mg group, 1 of 10 subjects (10.0%, 4 events) in the 60 mg group, and 4 of 20 subjects (20.0%, 7 events) in the allopurinol group.

4.(iii).A.(2) Japanese phase III studies

4.(iii).A.(2).1) Double-blind allopurinol-controlled comparative study (5.3.5.1-4, Study TMX-67-[redacted] [redacted] 20[redacted] to [redacted] 20[redacted])

A randomized, double-blind, allopurinol-controlled, comparative study was conducted to evaluate the efficacy and safety of febuxostat in patients with hyperuricemia including gout[40] (target sample size, 240 subjects [120/group]).

For the first 12 days, subjects received orally febuxostat 10 mg qd in the febuxostat group or allopurinol 100 mg qd in the allopurinol group after breakfast. Subsequently, febuxostat 40 mg qd was administered orally after breakfast in the febuxostat group, and allopurinol 100 mg bid (200 mg/day) was administered orally after morning and evening meals in the allopurinol group. The duration of treatment was 8 weeks.

Among all 244 treated subjects, 243 subjects (122 in the febuxostat group, 121 in the allopurinol group) were included in safety analysis. Excluded was 1 subject in the allopurinol group who mistakenly received febuxostat. Of those, 242 subjects were included in the FAS, in which primary efficacy was assessed. Excluded was 1 subject in the allopurinol group for whom serum urate data were not available A total of 8 subjects discontinued the study; the reasons included subject's request in 4 subjects (1 in the febuxostat group, 3 in the allopurinol group), an adverse event, wrong study drug administered, markedly low baseline serum urate values, and other reasons in 1 subject each in the allopurinol group.

The rate of change in serum urate level from baseline to Week 8, the primary efficacy endpoint, is shown in Table 16. The non-inferiority of febuxostat over allopurinol was demonstrated.

Table 16. Rate of change in serum urate level from baseline to Week 8 (FAS)

Treatment group (number of subjects analyzed)	Serum urate level			*P* value[b] (Non-inferiority test)
	Baseline (mg/dL)	Rate of change (%)	Between-group difference in the rate of change[a] [95% CI]	
Febuxostat (N = 122)	8.83 ± 1.32	-41.49 ± 12.12	-6.24 [-9.65, -2.84]	*P* < 0.001
Allopurinol (N = 120)	8.89 ± 1.24	-35.25 ± 14.67		

Mean ± SD; LOCF

a) The multiple regression model with treatment group, baseline serum urate level, and study site as explanatory variables

b) After subtracting the non-inferiority margin (5%) from the percent change in serum urate level at Week 8 for each subject in the allopurinol group, an analysis of variance with treatment group, baseline serum urate level, and study site as factors was performed at a one-sided significance level of 2.5%.

The percentage of subjects who achieved serum urate levels ≤6.0 mg/dL at Week 8, the secondary endpoint, was 82.0% (100 of 122 subjects) in the febuxostat group and 70.0% (84 of 120 subjects) in the allopurinol group.

Adverse events (including abnormal changes in laboratory values) were reported by 87 of 122 subjects (71.3%, 213 events) in the febuxostat group and 80 of 121 subjects (66.1%, 220 events) in the allopurinol group. Adverse events reported by ≥3% of subjects in either group are shown in Table 17.

[40] Key inclusion criteria: patients with serum urate levels ≥8.0 mg/dL. Key exclusion criteria: patients with gouty arthritis or whose gouty arthritis has resolved for <2 weeks at the examination before and at enrollment; patients who had received prohibited drugs including gout suppressants and antihyperuricemics within 2 weeks prior to pre-registration examination; patients with renal impairment (serum creatinine ≥1.5 mg/dL); patients with hepatic impairment (AST or ALT levels >2 times their local upper limit of normal).

Table 17. Adverse events reported by ≥3% of subjects in either group

Adverse event	Febuxostat (N = 122)	Allopurinol (N = 121)
Nasopharyngitis	14 (11.5)	18 (14.9)
Pharyngitis	4 (3.3)	1 (0.8)
Upper respiratory tract inflammation	5 (4.1)	10 (8.3)
Diarrhoea	4 (3.3)	9 (7.4)
Gouty arthritis	11 (9.0)	7 (5.8)
Thirst	1 (0.8)	4 (3.3)
ALT increased	4 (3.3)	4 (3.3)
AST increased	3 (2.5)	7 (5.8)
Urinary β_2-MG increased	8 (6.6)	7 (5.8)
Blood CK increased	7 (5.7)	5 (4.1)
Blood triglycerides increased	7 (5.7)	6 (5.0)
C-reactive protein increased	18 (14.8)	11 (9.1)
γ-GTP increased	3 (2.5)	5 (4.1)
Blood urine present	2 (1.6)	7 (5.8)
Red blood cells urine positive	2 (1.6)	6 (5.0)
White blood cell count increased	3 (2.5)	5 (4.1)
White blood cells urine positive	4 (3.3)	2 (1.7)
Protein urine present	1 (0.8)	5 (4.1)

Number of subjects who experienced the event (incidence, %); MedDRA/J Ver.12.0

Adverse drug reactions (including abnormal changes in laboratory values) were reported by 10 of 122 subjects (8.2%, 17 events) in the febuxostat group and 14 of 121 subjects (11.6%, 26 events) in the allopurinol group.

No deaths were reported. One serious adverse event of pain in extremity was reported by 1 subject in the febuxostat group, for which a causal relationship to the study drug was ruled out. One adverse event leading to study discontinuation (rash) was reported by 1 subject in the allopurinol group. Markedly abnormal laboratory values were reported by 1 subject in the febuxostat group (1 event of urinary β_2-MG increased) and 3 subjects in the allopurinol group (1 event each of blood glucose increased, white blood cell count increased, and protein urine present), for all of which a causal relationship to the study drug was ruled out.

Gouty arthritis was reported by 11 of 118 subjects (9.3%, 14 events) in the febuxostat group and 7 of 117 subjects (6.0%, 7 events) in the allopurinol group.[41]

4.(iii).A.(2).2) Placebo-controlled double-blind comparative study (5.3.5.1-3, Study TMX-67-[redacted] [[redacted] 20[redacted] to [redacted] 20[redacted]])

A randomized, double-blind, placebo-controlled, parallel-group comparative study was conducted to evaluate the efficacy and safety of febuxostat in patients with hyperuricemia including gout[42] (target sample size, 90 subjects [30/group]).

Subjects received orally placebo or febuxostat 20 or 40 mg qd after breakfast. Subjects in the febuxostat group received orally febuxostat 10 mg qd for the first 2 weeks, and then febuxostat 20 or 40 mg qd. The duration of treatment was 8 weeks.

All 102 treated subjects (33 in the placebo group, 35 in the febuxostat 20 mg group, 34 in the 40 mg group) were included in the FAS, in which primary efficacy and safety was assessed. A total of 2 subjects discontinued the study; the reasons included an adverse event for 1 subject (febuxostat 20 mg group) and subject's request for the other subject (febuxostat 40 mg group).

The percentage of subjects who achieved serum urate levels ≤6.0 mg/dL at Week 8, the primary efficacy endpoint, is shown in Table 18. There was a significant difference between each febuxostat group and the placebo group.

[41] The incidence is inconsistent with that shown in Table 17 because 8 subjects (4 each in the febuxostat and allopurinol groups) who received any anti-inflammatory analgesic treatment for ≥75% of study treatment duration for a purpose of other than treatment of gouty arthritis were excluded from calculation. No events of gouty arthritis were reported by the 8 subjects.

[42] See footnote 40.

Table 18. Percentage of subjects who achieved serum urate levels ≤6.0 mg/dL at Week 8 (FAS)

Treatment group (number of subjects analyzed)	Percentage of subjects who achieved serum urate levels of ≤6.0 mg/dL	*P* value[a)]
Placebo (N = 33)	0.0 (0/33)	-
Febuxostat 20 mg (N = 35)	45.7 (16/35)	$P = 0.007$
Febuxostat 40 mg (N = 34)	91.2 (31/34)	$P < 0.001$

Achievement rate (%) (number of subjects who achieved the serum urate levels/number of subjects analyzed); LOCF

a) Test (Wald's test) for regression coefficient in a logistic regression model[43] with treatment group and baseline serum urate level as covariates, adjusted for multiplicity using closed testing procedure, with a one-sided significance level of 2.5%.

The rate of change in serum urate level from baseline to Week 8, the secondary endpoint, is shown in Table 19.

Table 19. Rate of change in serum urate level from baseline to Week 8 (FAS)

Treatment group (number of subjects analyzed)	Serum urate level	
	Baseline (mg/dL)	Rate of change (%)
Placebo (N = 33)	8.95 ± 1.13	-1.7 ± 12.0
Febuxostat 20 mg (N = 35)	8.51 ± 0.88	-27.7 ± 11.6
Febuxostat 40 mg (N = 34)	8.52 ± 1.00	-43.7 ± 13.5

Mean ± SD; LOCF

Adverse events (including abnormal changes in laboratory values) were reported by 26 of 33 subjects (78.8%, 67 events) in the placebo group, 27 of 35 subjects (77.1%, 93 events) in the febuxostat 20 mg group, and 23 of 34 subjects (67.6%, 74 events) in the 40 mg group. Adverse events reported by ≥2 subjects in any group are shown in Table 20.

Table 20. Adverse events reported by ≥2 subjects in any group

Adverse event	Placebo (N = 33)	Febuxostat 20 mg (N = 35)	Febuxostat 40 mg (N = 34)
Gastroenteritis	0 (0.0)	0 (0.0)	2 (5.9)
Nasopharyngitis	4 (12.1)	7 (20.0)	3 (8.8)
Pharyngitis	4 (12.1)	4 (11.4)	1 (2.9)
Cough	0 (0.0)	2 (5.7)	0 (0.0)
Upper respiratory tract inflammation	2 (6.1)	4 (11.4)	2 (5.9)
Diarrhoea	1 (3.0)	4 (11.4)	1 (2.9)
Gouty arthritis	4 (12.1)	2 (5.7)	6 (17.6)
Injury	0 (0.0)	0 (0.0)	2 (5.9)
ALT increased	4 (12.1)	3 (8.6)	2 (5.9)
AST increased	2 (6.1)	2 (5.7)	3 (8.8)
Urinary β_2-MG increased	3 (9.1)	3 (8.6)	3 (8.8)
NAG increased	1 (3.0)	2 (5.7)	1 (2.9)
Blood cholesterol increased	0 (0.0)	0 (0.0)	2 (5.9)
Blood CK increased	5 (15.2)	5 (14.3)	2 (5.9)
Blood TSH increased	1 (3.0)	2 (5.7)	2 (5.9)
Blood triglycerides increased	2 (6.1)	8 (22.9)	3 (8.8)
C-reactive protein increased	9 (27.3)	11 (31.4)	2 (5.9)
γ-GTP increased	3 (9.1)	4 (11.4)	1 (2.9)
White blood cell count increased	2 (6.1)	1 (2.9)	1 (2.9)
Neutrophil percentage increased	0 (0.0)	1 (2.9)	2 (5.9)
Lymphocyte percentage decreased	0 (0.0)	1 (2.9)	3 (8.8)
Reticulocyte percentage increased	2 (6.1)	0 (0.0)	0 (0.0)

Number of subjects who experienced the event (incidence, %); MedDRA/J Ver.12.0

Adverse drug reactions (including abnormal changes in laboratory values) were reported by 2 of 33 subjects (6.1%, 2 events) in the placebo group, 4 of 35 subjects (11.4%, 6 events) in the febuxostat 20 mg group, and 7 of 34 subjects (20.6%, 12 events) in the 40 mg group.

No deaths were reported. One serious adverse event of gouty arthritis was reported by 1 subject in the febuxostat 40 mg group, for which a causal relationship to the study drug was ruled out. One subject in

[43] Comparison between the febuxostat 20 mg and the placebo groups was performed not including the febuxostat 40 mg group in the logistic regression model, and comparison between the febuxostat 40 mg and the placebo groups was performed not including the febuxostat 20 mg group in the model.

the febuxostat 20 mg group who experienced chest pain was withdrawn from the study because treatment with a prohibited concomitant drug was considered necessary to prevent thrombosis, the probable cause of the chest pain.

Gouty arthritis was reported by 4 of 32 subjects (12.5%, 5 events) in the placebo group, 2 of 34 subjects (5.9%, 2 events) in the febuxostat 20 mg group, and 6 of 34 subjects (17.6%, 12 events) in the 40 mg group.[44]

4.(iii).A.(3) Japanese long-term treatment studies

4.(iii).A.(3).1) Long-term treatment study (5.3.5.2-1, Study TMX-67-[redacted])

An open-label study was conducted to evaluate the efficacy and safety of 28- and 52-week treatment with febuxostat in patients with hyperuricemia including gout[45] (target sample size; 200 subjects in the 28-week treatment group, 100 subjects in the 52-week treatment group).

Subjects received orally febuxostat 10 mg qd after breakfast for the first 4 weeks, and subsequently, the dose be modified in a stepwise manner (10 mg ↔ 20 mg ↔ 40 mg) at the investigator's discretion to maintain serum urate levels within the range of 4 to 6 mg/dL. The duration of treatment was 28 or 52 weeks.[46]

All 303 treated subjects (171 in the 28-week treatment group, 132 in the 52-week treatment group) were included in safety analysis, and of these, 299 subjects were included in the per protocol set (PPS), in which primary efficacy was assessed. Excluded were 4 subjects with violation of inclusion (2 subjects) or exclusion (2 subjects) criteria in the 28-week treatment group. A total of 21 subjects discontinued the study; the reasons included subject's request in 11 subjects (5 in the 28-week treatment group, 6 in the 52-week treatment group), safety considerations in 6 subjects (5 in the 28-week treatment group, 1 in the 52-week treatment group), and other reasons in 4 subjects (3 in the 28-week treatment group, 1 in the 52-week treatment group).

The serum urate levels at Weeks 28 and 52 are shown in Table 21, and the time courses of rate of change in serum urate level and percentage of subjects who achieved serum urate levels ≤6.0 mg/dL are shown in Figures 1 and 2, respectively. At the end of treatment (Week 28 or 52), the dose of febuxostat was 10 mg in 34 and 23 subjects; 20 mg in 63 and 46 subjects; and 40 mg in 57 and 55 subjects in the 28-week treatment group and in the 52-week treatment group, respectively.

Table 21. Serum urate levels at Weeks 28 and 52 (PPS)

Treatment group	Serum urate level (mg/dL)		
	Baseline	Week 28	Week 52
28-Week treatment	9.12 ± 1.24 (167)	5.85 ± 0.92 (154)	-
52-Week treatment	8.96 ± 1.04 (132)	5.96 ± 0.82 (125)	5.77 ± 0.94 (124)

Mean ± SD (number of subjects)

[44] The incidence is inconsistent with that shown in Table 20 because 2 subjects (1 each in the placebo and the febuxostat 20 mg groups) who received any anti-inflammatory analgesic treatment for ≥75% of study treatment duration for a purpose of other than treatment of gouty arthritis were excluded from calculation. No events of gouty arthritis were reported by the 2 subjects.

[45] See footnote 34.

[46] The duration of treatment (28 or 52 weeks) was selected after discussion between the investigator and the applicant at each study site separately. At some study sites, subjects selected the duration of treatment for themselves.

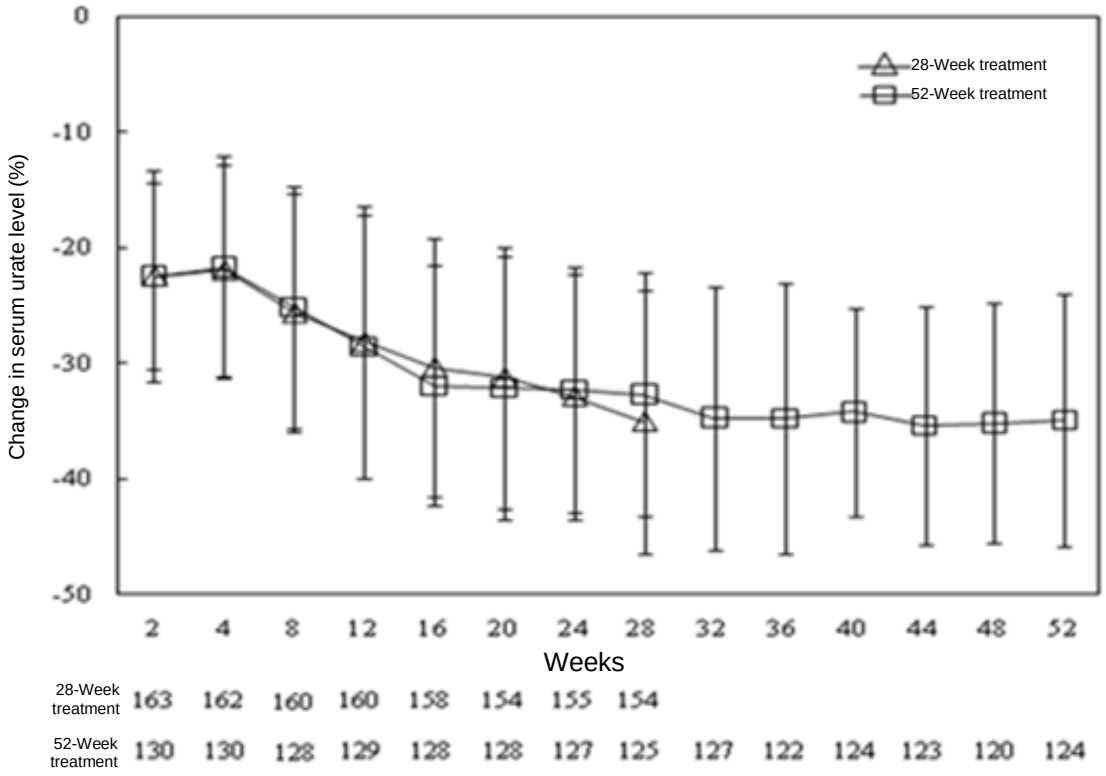

Figure 1. Time courses of rate of change in serum urate level (mean ± SD)

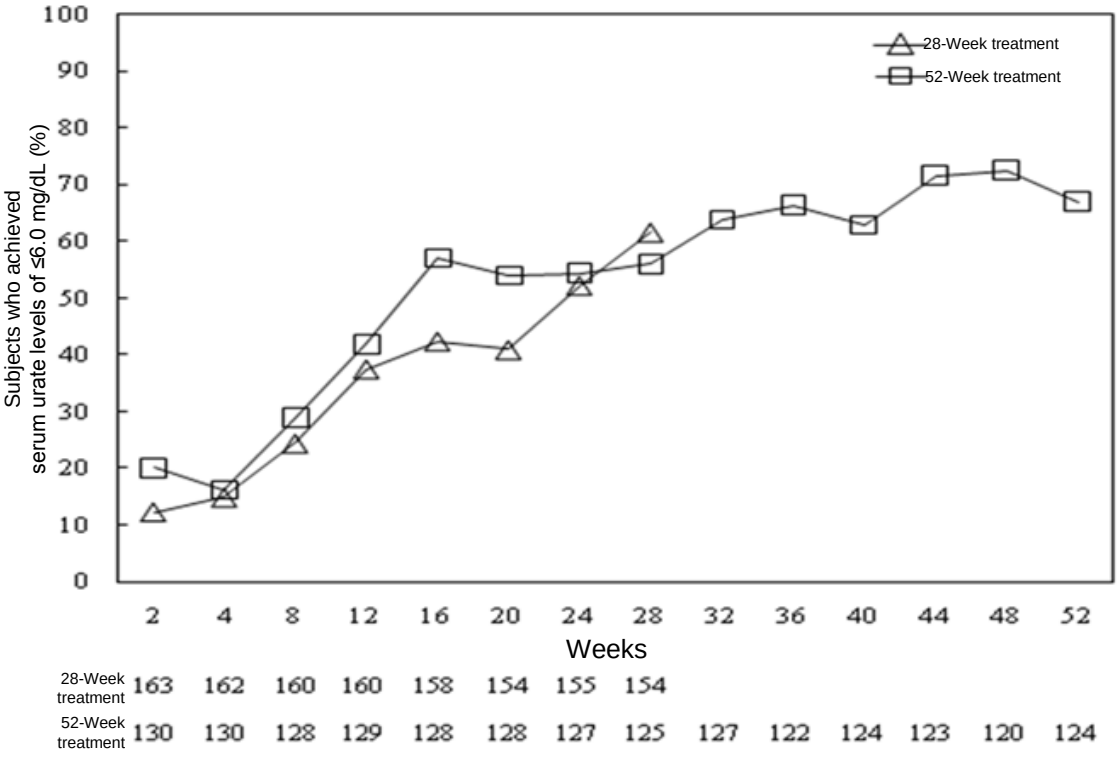

Figure 2. Time course of percentage of subjects who achieved serum urate levels ≤6.0 mg/dL

Adverse events (including abnormal changes in laboratory values) were reported by 140 of 171 subjects (81.9%, 550 events) in the 28-week treatment group and 129 of 132 subjects (97.7%, 878 events) in the 52-week treatment group. Adverse events (excluding abnormal changes in laboratory values) reported by ≥3% of subjects in either group are shown in Table 22.

Table 22. Adverse events reported by ≥3% of subjects in either group (excluding abnormal changes in laboratory values)

Adverse event	28-Week treatment (N = 171)	52-Week treatment (N = 132)
Bronchitis	3 (1.8)	4 (3.0)
Nasopharyngitis	41 (24.0)	65 (49.2)
Pharyngitis	8 (4.7)	4 (3.0)
Dizziness	4 (2.3)	9 (6.8)
Headache	7 (4.1)	7 (5.3)
Hypoaesthesia	4 (2.3)	6 (4.5)
Cough	1 (0.6)	6 (4.5)
Rhinorrhoea	2 (1.2)	4 (3.0)
Upper respiratory tract inflammation	10 (5.8)	16 (12.1)
Oropharyngeal pain	5 (2.9)	8 (6.1)
Abdominal discomfort	2 (1.2)	6 (4.5)
Abdominal pain	2 (1.2)	5 (3.8)
Abdominal pain upper	2 (1.2)	4 (3.0)
Diarrhoea	13 (7.6)	17 (12.9)
Enterocolitis	0 (0.0)	5 (3.8)
Nausea	1 (0.6)	5 (3.8)
Stomatitis	2 (1.2)	4 (3.0)
Toothache	1 (0.6)	4 (3.0)
Erythema	1 (0.6)	5 (3.8)
Rash	9 (5.3)	5 (3.8)
Urticaria	2 (1.2)	4 (3.0)
Arthralgia	8 (4.7)	14 (10.6)
Back pain	5 (2.9)	11 (8.3)
Gouty arthritis	28 (16.4)	29 (22.0)
Musculoskeletal pain	2 (1.2)	4 (3.0)
Myalgia	1 (0.6)	5 (3.8)
Pain in extremity	7 (4.1)	10 (7.6)
Limb discomfort	1 (0.6)	5 (3.8)
Chest pain	1 (0.6)	4 (3.0)
Pyrexia	1 (0.6)	4 (3.0)

Number of subjects who experienced the event (incidence, %); MedDRA/J Ver.12.0

Adverse drug reactions (including abnormal changes in laboratory values) were reported by 39 of 171 subjects (22.8%, 78 events) in the 28-week treatment group and 29 of 132 subjects (22.0%, 60 events) in the 52-week treatment group.

No deaths were reported. A total of 4 serious adverse events (putamen haemorrhage, ligament rupture, tonsillitis, and upper respiratory tract inflammation in 1 subject each) were reported by 4 subjects in the 28-week treatment group and 3 serious adverse events (osteoarthritis, cholestasis/γ-GTP increased in 1 subject each) were reported by 2 subjects in the 52-week treatment group, for all of which a causal relationship to the study drug was ruled out. Non-serious adverse events leading to study discontinuation were reported by 5 subjects in the 28-week treatment group (8 events; rash, hypoaesthesia/pain in extremity, rash generalised, AST increased/ALT increased, electrocardiogram abnormal/heart rate decreased) and 2 subjects in the 52-week treatment group (7 events; AST increased/ALT increased/blood LDH increased, AST increased/ALT increased/blood LDH increased/γ-GTP increased).

Gouty arthritis was reported by 27 of 163 subjects (16.6%, 56 events) in the 28-week treatment group, and 29 of 129 subjects (22.5%, 63 events) in the 52-week treatment group.[47] The incidence of gouty arthritis was highest between Weeks 0 and 4 during the study in both groups (9.2% [15 of 163 subjects], 16 events in the 28-week treatment group; 7.8% [10 of 129 subjects], 11 events in the 52-week treatment group). The incidence was then gradually decreased as the serum urate levels were better controlled, reaching 1.3% (2 of 153 subjects [2 events]) in the 28-week treatment group and 4.0% (5 of 125 subjects [5 events]) in the 52-week treatment group between Weeks 24 and 28, and 1.6% (2 of 122 subjects [2 events]) in the 52-week treatment group between Weeks 48 and 52.

[47] The incidence is inconsistent with that shown in Table 22 because 11 subjects (8 in the 28-week treatment group, 3 in the 52-week treatment group) who received colchicine or any anti-inflammatory analgesic treatment for ≥75% of study treatment duration for a purpose of other than treatment of gouty arthritis were excluded from calculation.

The incidence of abnormal changes in laboratory values warranting clinical attention in the 28-week (171 subjects) and 52-week (132 subjects) treatment groups were as follows, respectively: ALT increased, 9.9% (17 subjects) and 14.4% (19 subjects); AST increased, 7.0% (12 subjects) and 9.8% (13 subjects); γ-GTP increased, 10.5% (18 subjects) and 16.7% (22 subjects); and blood LDH increased, 2.3% (4 subjects) and 6.1% (8 subjects) for liver function-related parameters; urinary β_2-MG increased, 4.7% (8 subjects) and 9.1% (12 subjects); NAG increased, 3.5% (6 subjects) and 6.1% (8 subjects) for renal function-related parameters; and blood CK increased, 10.5% (18 subjects) and 15.2% (20 subjects); C-reactive protein increased, 18.1% (31 subjects) and 32.6% (43 subjects); and blood TSH increased, 2.9% (5 subjects) and 3.8% (5 subjects) for other parameters.

4.(iii).A.(3).2) Long-term treatment study (additional study) (5.3.5.2-2, Study TMX-67-[redacted] [redacted] 20[redacted] to [redacted] 20[redacted])

An open-label study was conducted to confirm the safety and efficacy of long-term treatment with febuxostat in patients with hyperuricemia including gout[48] (target sample size, ≥30 subjects shifting to febuxostat 60 mg).

Subjects initially received orally febuxostat 10 mg qd after breakfast, and subsequently, the dose was increased to 20 mg from Week 3, 40 mg from Week 7, and 60 mg from Week 15 (only in subjects with serum urate levels >6.0 mg/dL at Week 10; the dose was maintained at 40 mg in subjects who achieved serum urate levels ≤6.0 mg/dL) (The "40 mg group" and "60 mg group" consist of subjects who received 40 and 60 mg of febuxostat from Week 15, respectively). The duration of treatment was 52 weeks.

Of all 178 treated subjects, 171 subjects (131 in the febuxostat 40 mg group,[49] 40 in the 60 mg group[50]) were included in safety analysis. Excluded were 7 subjects enrolled through a recruitment procedure not approved by the institutional review board, a GCP violation. Of those 171 subjects, 169 subjects were included in the FAS, in which primary efficacy was assessed. Excluded were 2 subjects in the febuxostat 40 mg group with no serum urate level data after baseline. A total of 13 subjects discontinued the study during the first 14 weeks of treatment, and the reasons included investigator's decision in 6 subjects, subject's wish in 3 subjects, baseline serum urate ≤7.0 mg/dL in 3 subjects, missing dose on the day before Week 10 blood sampling and serum urate >6.0 mg/dL in 1 subject. A total of 18 subjects discontinued the study at Week 15 or later, and the reasons included subject's wish in 7 subjects (5 in the febuxostat 40 mg group, 2 in the 60 mg group), personal reasons in 6 subjects (3 each in the 40 and 60 mg groups), missing doses on ≥8 consecutive days in 3 subjects (febuxostat 40 mg group), and an adverse event in 2 subjects (febuxostat 40 mg group).

The serum urate levels at Weeks 26 and 52 are shown in Table 23, and the time courses of rate of change in serum urate level and percentage of subjects who achieved serum urate levels ≤6.0 mg/dL are shown in Figures 3 and 4, respectively.

Table 23. Serum urate levels at Weeks 26 and 52 (FAS)

Treatment group	Serum urate level (mg/dL)		
	Baseline	Week 26	Week 52
Febuxostat 40 mg	9.59 ± 1.06 (129)	5.01 ± 0.92 (118)	5.17 ± 1.11 (110)
Febuxostat 60 mg	10.60 ± 1.38 (40)	5.58 ± 1.13 (35)	5.29 ± 0.81 (32)

Mean ± SD (number of subjects)

[48] Key inclusion criteria: patients with serum urate levels ≥9.0 mg/dL. Key exclusion criteria: patients presenting with gouty arthritis or whose gouty arthritis has resolved for <13 days at the examination before and at enrollment; patients who have received prohibited drugs including gout suppressants and antihyperuricemics within 13 days prior to pre-registration examination; patients with renal impairment (serum creatinine ≥1.8 mg/dL); patients with hepatic impairment (AST or ALT levels of >2 times the upper limit of normal).

[49] Subjects who received febuxostat 40 mg at Week 15 or later

[50] Subjects who received febuxostat 60 mg at Week 15 or later

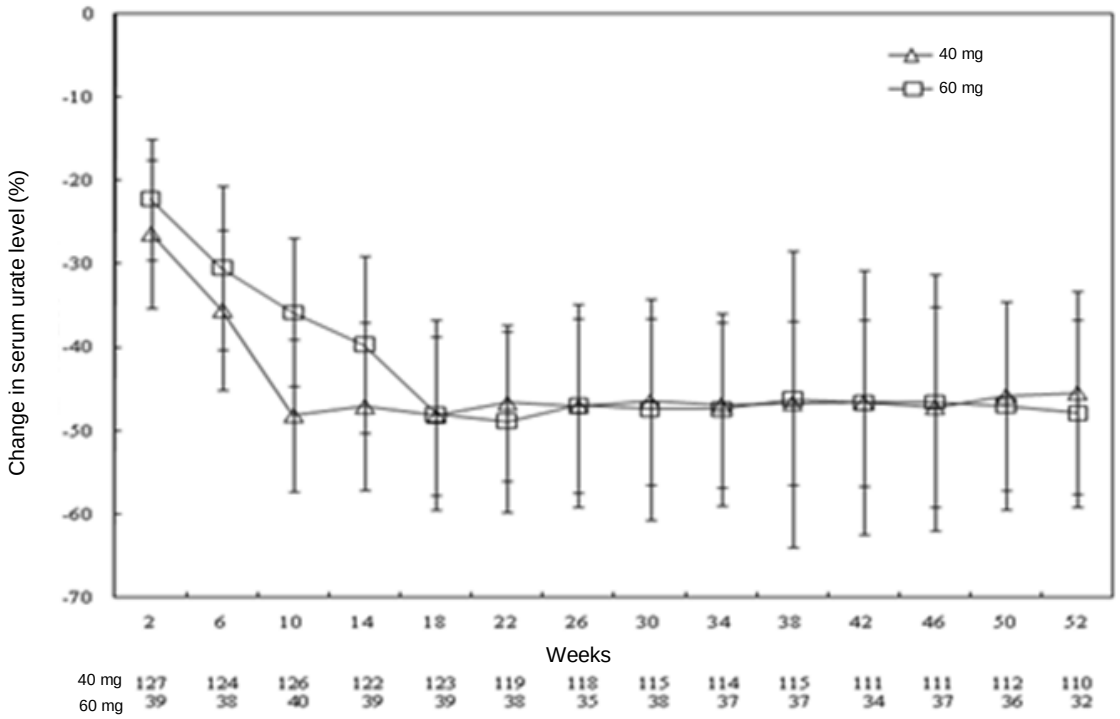

Figure 3. Time course of rate of change in serum urate level (mean ± SD)

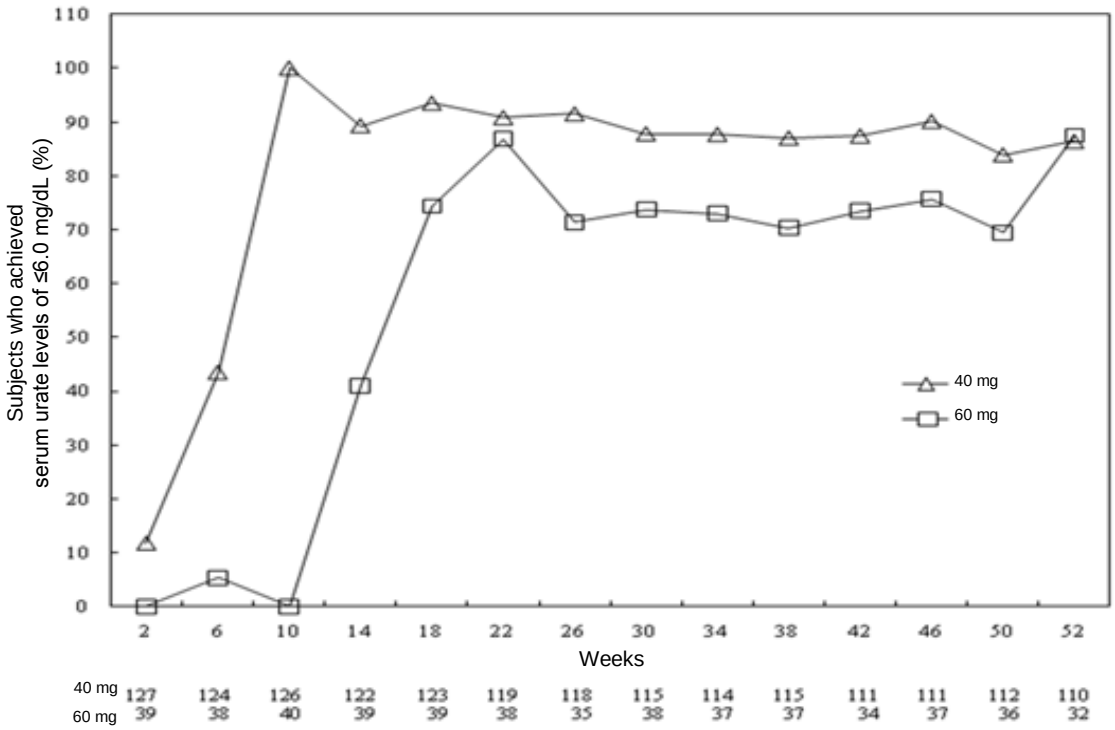

Figure 4. Time course of percentage of subjects who achieved serum urate levels ≤6.0 mg/dL

Adverse events (including abnormal changes in laboratory values) were reported by 122 of 131 subjects (93.1%, 574 events) in the 40 mg group and 38 of 40 subjects (95.0%, 178 events) in the 60 mg group. Adverse events (excluding abnormal changes in laboratory values) reported by ≥3% of subjects in either group are shown in Table 24.

Table 24. Adverse events reported by ≥3% of subjects in either group (excluding abnormal changes in laboratory values)

Adverse event	Febuxostat 40 mg (N = 131)	Febuxostat 60 mg (N = 40)
Bronchitis	8 (6.1)	0 (0.0)
Gastroenteritis	3 (2.3)	4 (10.0)
Influenza	6 (4.6)	1 (2.5)
Nasopharyngitis	52 (39.7)	14 (35.0)
Pharyngitis	7 (5.3)	2 (5.0)
Oral herpes	6 (4.6)	1 (2.5)
Seasonal allergy	4 (3.1)	1 (2.5)
Vertigo	4 (3.1)	0 (0.0)
Hypertension	5 (3.8)	5 (12.5)
Abdominal discomfort	3 (2.3)	3 (7.5)
Abdominal pain	4 (3.1)	2 (5.0)
Abdominal pain upper	5 (3.8)	1 (2.5)
Constipation	2 (1.5)	2 (5.0)
Dental caries	3 (2.3)	2 (5.0)
Diarrhoea	8 (6.1)	1 (2.5)
Hepatic function abnormal	7 (5.3)	1 (2.5)
Hepatic steatosis	2 (1.5)	2 (5.0)
Dermatitis contact	1 (0.8)	2 (5.0)
Eczema	6 (4.6)	2 (5.0)
Arthralgia	16 (12.2)	7 (17.5)
Back pain	5 (3.8)	2 (5.0)
Gouty arthritis	27 (20.6)	10 (25.0)
Myalgia	6 (4.6)	2 (5.0)
Pain in extremity	7 (5.3)	5 (12.5)
Periarthritis	6 (4.6)	1 (2.5)
Limb discomfort	6 (4.6)	4 (10.0)
Contusion	7 (5.3)	1 (2.5)

Number of subjects who experienced the event (incidence, %); MedDRA/J Ver.12.0

Adverse drug reactions (including abnormal changes in laboratory values) were reported by 49 of 131 subjects (37.4%, 111 events) in the 40 mg group and 14 of 40 subjects (35.0%, 46 events) in the 60 mg group.

No deaths were reported. A total of 4 serious adverse events (gastric ulcer haemorrhage, spinal column stenosis, sinusitis, and spinal osteoarthritis in 1 subject each) were reported by 4 subjects in the 40 mg group, for all of which a causal relationship to the study drug was ruled out. A non-serious adverse event leading to study discontinuation (anaemia) was reported by 1 subject in the 40 mg group, for which a causal relationship to the study drug was ruled out.

Gouty arthritis was reported by 27 of 131 subjects (20.6%, 52 events) in the 40 mg group and 10 of 40 subjects (25.0%, 26 events) in the 60 mg group. During the study, the incidence of gouty arthritis was highest between Weeks 6 and 10 (6.5% [11 of 168 subjects], 13 events: 5.5% [7 of 128 subjects], 8 events in the 40 mg group; 10.0% [4 of 40 subjects], 5 events in the 60 mg group), second highest between Weeks 18 to 22 (5.6% [9 of 161 subjects], 12 events: 4.9% [6 of 122 subjects], 8 events in the 40 mg group; 7.7% [3 of 39 subjects], 4 events in the 60 mg group), and third highest between Weeks 38 to 42 (4.5% [7 of 157 subjects], 7 events: 4.2% [5 of 119 subjects], 5 events in the 40 mg group, 5.3% [2 of 38 subjects], 2 events in the 60 mg group).

The incidence of abnormal changes in laboratory values warranting clinical attention in the 40 mg (131 subjects) and 60 mg (40 subjects) groups, respectively, were as follows: AST increased, 3.1% (4 subjects) and 0%; γ-GTP increased, 5.3% (7 subjects) and 2.5% (1 subject) for liver function-related parameters; urinary β_2-MG increased, 6.9% (9 subjects) and 5.0% (2 subjects) for renal function-related parameters; and blood CK increased, 5.3% (7 subjects) and 7.5% (3 subject); and C-reactive protein increased, 6.9% (9 subjects) and 12.5% (5 subjects) for other parameters.

4.(iii).B Outline of the review by PMDA

4.(iii).B.(1) Clinical positioning of febuxostat

The applicant's explanation on clinical significance of febuxostat:

The *Japanese Treatment Guideline* 2nd ed. states that the treatment goal for hyperuricemia including gout is to reduce the incidence of gouty arthritis and achieve tophus regression by maintaining serum urate levels ≤6.0 mg/dL. Efficacy of febuxostat was evaluated in 5 Japanese randomized parallel group studies (Studies TMX-67-[redacted], TMX-67-[redacted], TMX-67-[redacted], TMX-67-[redacted], and TMX-67-[redacted] [5 Japanese clinical studies]). The percentage of subjects who achieved serum urate levels ≤6.0 mg/dL was 77.4% to 91.2% in the febuxostat 40 mg group and 83.3% to 88.9% in the 60 mg group. In 2 Japanese long-term treatment studies (Studies TMX-67-[redacted] and TMX-67-[redacted] [2 Japanese long-term treatment studies]), serum urate levels were generally maintained at ≤6.0 mg/dL (Figures 2 and 4), and the incidence of gouty arthritis was decreased with increasing treatment duration [see "4.(iii).A.(3) Japanese long-term treatment studies"]. In addition, the results from foreign drug interaction studies demonstrated a low likelihood of drug-drug interactions of febuxostat with potential concomitant drugs including colchicine, antacids, indomethacin, hydrochlorothiazide, warfarin, and theophylline [see "4.(ii).A.(2).4) Drug interactions"]. Although, as compared with C_{max} and $AUC_{0\text{-}24h}$ of unchanged febuxostat in subjects with normal renal function, those in patients with mild renal impairment were approximately 1.0 and 1.5 times, respectively, and those in patients with moderate renal impairment were approximately 1.3 and 1.7 times, respectively (Study TMX-67-[redacted]), the results from Japanese clinical studies demonstrated no impact of renal impairment of moderate or lower severity on the efficacy and safety of febuxostat [see "4.(iii).B.(6).1) Patients with renal impairment"]. Consequently, febuxostat is expected to reduce the incidence of gouty arthritis and induce tophus regression by lowering serum urate levels to ≤6.0 mg/dL over a long period of time. Febuxostat can also offer a new treatment option, with no need for dose adjustment even in patients with renal impairment of moderate or lower severity and limited interaction risk with potential concomitant drugs.

PMDA's view:

Febuxostat can provide a new option of uric acid production inhibitor based on the following facts: allopurinol is only one approved drug classified as a uric acid production inhibitor, in which febuxostat is classified; the data from an allopurinol-controlled phase III study of febuxostat (Study TMX-67-[redacted]) etc., have demonstrated the efficacy of febuxostat [see "4.(iii).B.(2) Efficacy"]; the safety of febuxostat is acceptable at present [see "4.(iii).B.(3) Safety"]; and treatment with febuxostat without dose adjustment in patients with renal impairment of moderate or lower severity has posed no major safety problems [see "4.(iii).B.(6).1) Patients with renal impairment"].

4.(iii).B.(2) Efficacy

PMDA reviewed the difference in efficacy of febuxostat between clinical diagnosis of gout and hyperuricemia on the basis of the results of allopurinol-controlled double-blind comparative study (Study TMX-67-[redacted]). The percentage of subjects who achieved serum urate levels ≤6.0 mg/dL and the rate of change in serum urate level from baseline in this study are shown in Table 25. There was a difference in baseline serum urate levels between gout and hyperuricemia subgroups. However, the baseline serum urate levels were not markedly different between the febuxostat 40 mg and allopurinol groups among both subgroups, and the between-group difference (febuxostat 40 mg versus allopurinol) in the percentage of subjects who achieved serum urate levels ≤6.0 mg/dL or the rate of change in serum urate level from baseline was similar between the 2 subgroups.

Table 25. Percentage of subjects who achieved serum urate levels ≤6.0 mg/dL and rate of change in serum urate level from baseline by clinical diagnosis (Study TMX-67-[redacted])

Clinical diagnosis	Treatment group	Number of subjects	Serum urate level		
			Baseline (mg/dL)	Percentage of subjects who achieved serum urate levels ≤6.0 mg/dL	Rate of change (%)
Gout	Allopurinol	59	9.20 ± 0.15	62.7	-35.12 ± 2.03
	Febuxostat 40 mg	54	9.31 ± 0.20	72.2	-39.73 ± 1.50
Hyperuricemia	Allopurinol	61	8.60 ± 0.16	77.0	-35.37 ± 1.77
	Febuxostat 40 mg	68	8.44 ± 0.13	89.7	-42.88 ± 1.55

Mean ± standard error

Study TMX-67-[redacted] showed non-inferiority of the febuxostat 40 mg/day over the allopurinol 200 mg/day, but the incidence of gouty arthritis was higher in the febuxostat group than in the allopurinol group. The initial regulatory application for febuxostat was withdrawn because it was concluded that appropriate dose (dose escalation scheme) of febuxostat had yet to be established from a safety viewpoint (development of gouty arthritis). Subsequently, additional studies with a new dose escalation protocol were conducted. In order to confirm the efficacy of febuxostat in the new dose escalation studies, the data of a placebo-controlled dose-response study (Study TMX-67-[redacted]) and allopurinol-controlled exploratory study (Study TMX-67-[redacted]), both based on the new dose escalation protocol, were reviewed in comparison with the data of Study TMX-67-[redacted] conducted based on the original dose escalation protocol. The rate of change in serum urate level from baseline and the percentage of subjects who achieved serum urate levels ≤6.0 mg/dL in the 3 studies are shown in Table 26.

Table 26. Rate of change in serum urate level from baseline and percentage of subjects who achieved serum urate levels ≤6 mg/dL

	TMX-67-[redacted] (8-week treatment)	TMX-67-[redacted] (16-week treatment)	TMX-67-[redacted] (16-week treatment)
Rate of change in serum urate level			
Placebo	-	-2.07 ± 12.60 (n = 38)	-
Febuxostat 20 mg/day	-	-29.65 ± 11.50 (n = 43)	-
Febuxostat 40 mg/day	-41.49 ± 12.12 (n = 122)	-40.59 ± 15.78 (n = 41)	-42.96 ± 13.33 (n = 10)
Febuxostat 60 mg/day	-	-48.35 ± 17.93 (n = 36)	-52.47 ± 9.79 (n = 9)
Febuxostat 80 mg/day	-	-52.02 ± 17.49 (n = 41)	-
Allopurinol (200 mg/day)	-35.25 ± 14.67 (n = 120)	-	-
Allopurinol (300 mg/day)	-	-	-36.55 ± 18.59 (n = 19)
Percentage of subjects who achieved serum urate levels ≤6 mg/dL			
Placebo	-	2.6 (n = 38)	-
Febuxostat 20 mg/day	-	46.5 (n = 43)	-
Febuxostat 40 mg/day	82.0 (n = 122)	82.9 (n = 41)	90.0 (n = 10)
Febuxostat 60 mg/day	-	83.3 (n = 36)	88.9 (n = 9)
Febuxostat 80 mg/day	-	87.8 (n = 41)	-
Allopurinol (200 mg/day)	70.0 (n = 120)	-	-
Allopurinol (300 mg/day)	-	-	73.7 (n = 19)

Mean ± SD

Febuxostat showed a persistent efficacy throughout the 52-week treatment period in a long-term treatment study (Study TMX-67-[redacted]) conducted based on the new dose escalation protocol as evidenced by the maximum rate of change in serum urate level in the 40 and 60 mg groups (-48.25% at Week 18 and -45.47% at Week 52 in the 40 mg group, -48.92% at Week 22 and -47.94% at Week 52 in the 60 mg group) (Figure 3). In addition, evaluation in terms of clinical diagnosis revealed that the percentage of subjects who achieved serum urate levels ≤6.0 mg/dL at the end of treatment in this study was 81.2% (95 of 117 subjects) in the subgroup of subjects with gout and 92.3% (48 of 52 subjects) in the subgroup of subjects with hyperuricemia, showing a high efficacy, and that the rate of change in serum urate level from baseline (mean ± SD) was -47.12% ± 12.78% in the subgroup of subjects with gout and -44.94% ± 9.96% in the subgroup of subjects with hyperuricemia, showing no substantial difference between the 2 subgroups.

PMDA's view:
The efficacy of febuxostat in patients with hyperuricemia has been demonstrated based on a comprehensive review of the following findings: (i) although the efficacy was evaluated based on the original dose escalation protocol, non-inferiority of febuxostat over allopurinol has been demonstrated for the rate of change in serum urate level from baseline to Week 8, the primary endpoint, in Study TMX-67-[redacted] (Table 16); (ii) a significant difference between each febuxostat group and the placebo group was found in the percentage of subjects who achieved serum urate levels ≤6.0 mg/dL at Week 16, the primary endpoint, in Study TMX-67-[redacted] conducted based on the new dose escalation protocol (Table 11); (iii) no substantial difference was observed in the percentage of subjects who achieved serum urate levels ≤6.0 mg/dL or the rate of change in serum urate level from baseline between Study TMX-67-[redacted] conducted based on the original dose escalation protocol and Studies TMX-67-[redacted] and TMX-67-[redacted] conducted based on the new dose escalation protocol, although rigorous comparison is difficult due to inconsistency in study design (Table 26); and (iv) a long-term treatment study (Study TMX-67-[redacted])

conducted based on the new dose escalation protocol showed a persistent efficacy (Table 23 and Figures 3 and 4).

4.(iii).B.(3) Safety

The incidence of adverse events and adverse drug reactions (both including abnormal changes in laboratory values) in the 5 Japanese clinical studies are listed in Table 27. Although comparison is difficult for Study TMX-67-[redacted] due to the limited sample size, no substantial difference in the incidence of adverse events was found between the febuxostat group and the placebo or allopurinol group in the remaining 4 studies. The incidence of adverse drug reactions tended to be generally higher in the febuxostat group than in the placebo and allopurinol groups in the 4 studies excluding Study TMX-67-[redacted], but serious adverse events for which a causal relationship to the study drug could not be ruled out were not reported in the 5 studies.

Table 27. Incidence of adverse events and adverse drug reactions (both including abnormal changes in laboratory values) in the 5 Japanese clinical studies

	TMX-67-[redacted] (8-week treatment)	TMX-67-[redacted] (8-week treatment)	TMX-67-[redacted] (8-week treatment)	TMX-67-[redacted] (16-week treatment)	TMX-67-[redacted] (16-week treatment)
Overall adverse events (including abnormal changes in laboratory values)					
Placebo	22/28 (78.6)	-	26/33 (78.8)	22/38 (57.9)	-
Febuxostat 10 mg	19/29 (65.5)	-	-	-	-
Febuxostat 20 mg	22/29 (75.9)	-	27/35 (77.1)	27/43 (62.8)	-
Febuxostat 40 mg	24/31 (77.4)	87/122 (71.3)	23/34 (67.6)	25/41 (61.0)	8/10 (80.0)
Febuxostat 60 mg	-	-	-	24/36 (66.7)	5/10 (50.0)
Febuxostat 80 mg	-	-	-	25/41 (61.0)	-
Allopurinol	-	80/121 (66.1)	-	-	16/20 (80.0)
Overall adverse drug reactions (including abnormal changes in laboratory values)					
Placebo	2/28 (7.1)	-	2/33 (6.1)	7/38 (18.4)	-
Febuxostat 10 mg	8/29 (27.6)	-	-	-	-
Febuxostat 20 mg	5/29 (17.2)	-	4/35 (11.4)	10/43 (23.3)	-
Febuxostat 40 mg	5/31 (16.1)	10/122 (8.2)	7/34 (20.6)	12/41 (29.3)	6/10 (60.0)
Febuxostat 60 mg	-	-	-	5/36 (13.9)	2/10 (20.0)
Febuxostat 80 mg	-	-	-	12/41 (29.3)	-
Allopurinol	-	14/121 (11.6)	-	-	5/20 (25.0)

Number of subjects who experienced the event/number of subjects analyzed (incidence, %)

The incidence of adverse events and adverse drug reactions (both including abnormal changes in laboratory values) in the 2 Japanese long-term treatment studies (Studies TMX-67-[redacted] and TMX-67-[redacted]) were as follows: 81.9% (140 of 171) of subjects and 22.8% (39 of 171) of subjects, respectively, in the 28-week treatment group and 97.7% (129 of 132) of subjects and 22.0% (29 of 132) of subjects, respectively, in the 52-week treatment group in Study TMX-67-[redacted] (in which dose modification was permitted within the range of 10-40 mg); 93.1% (122 of 131) of subjects and 37.4% (49 of 131) of subjects, respectively, in the 40 mg group and 95.0% (38 of 40) of subjects and 35.0% (14 of 40) of subjects, respectively, in the 60 mg group in Study TMX-67-[redacted]. No serious adverse events for which a causal relationship to the study drug could not be ruled out were reported in either study.

PMDA has concluded that the safety of febuxostat is acceptable at present on the basis of data from the 5 Japanese clinical studies and the 2 Japanese long-term treatment studies described above, while further review was conducted regarding individual events including gouty arthritis and kidney/bladder-related adverse events in the following sections 4.(iii).B.(3).1) to 4.(iii).B.(3).6).

4.(iii).B.(3).1) Gouty arthritis

On the basis of incidence of gouty arthritis in the 5 Japanese clinical studies (Table 28), PMDA has concluded as follows:

Table 28. Incidence of gouty arthritis in the 5 Japanese clinical studies

	TMX-67-[redacted] (8-week treatment)	TMX-67-[redacted] (8-week treatment)	TMX-67-[redacted] (8-week treatment)	TMX-67-[redacted] (16-week treatment)	TMX-67-[redacted] (16-week treatment)
Gouty arthritis					
Placebo	1/28 (3.6)	-	4/33 (12.1)	2/38 (5.3)	-
Febuxostat 10 mg	5/29 (17.2)	-	-	-	-
Febuxostat 20 mg	6/29 (20.7)	-	2/35 (5.7)	4/43 (9.3)	-
Febuxostat 40 mg	7/31 (22.6)	11/122 (9.0)	6/34 (17.6)	3/41 (7.3)	1/10 (10.0)
Febuxostat 60 mg	-	-	-	3/36 (8.3)	1/10 (10.0)
Febuxostat 80 mg	-	-	-	9/41 (22.0)	-
Allopurinol	-	7/121 (5.8)	-	-	4/20 (20.0)
Gouty arthritis for which a causal relationship to the study drug could not be ruled out					
Placebo	0/28 (0.0)	-	0/33 (0.0)	2/38 (5.3)	-
Febuxostat 10 mg	4/29 (13.8)	-	-	-	-
Febuxostat 20 mg	2/29 (6.9)	-	0/35 (0.0)	4/43 (9.3)	-
Febuxostat 40 mg	2/31 (6.5)	4/122 (3.3)	4/34 (11.8)	3/41 (7.3)	1/10 (10.0)
Febuxostat 60 mg	-	-	-	3/36 (8.3)	1/10 (10.0)
Febuxostat 80 mg	-	-	-	8/41 (19.5)	-
Allopurinol	-	2/121 (1.7)	-	-	4/20 (20.0)

Number of subjects who experienced the event/number of subjects analyzed (incidence, %)

In Study TMX-67-[redacted] conducted based on the new dose escalation protocol, no substantial difference was observed between the placebo and febuxostat groups (excluding subjects receiving 80 mg, which exceeds the maximum proposed dose) in the incidence of gouty arthritis, which is commonly seen early during therapy and generally attributed to a rapid fall in serum urate levels. In Study TMX-67-[redacted], although evaluation of incidence was limited due to the small sample size, there was no tendency for the incidence to be a higher in the febuxostat group than in the allopurinol group. However, in Studies TMX-67-[redacted], TMX-67-[redacted], and TMX-67-[redacted] conducted based on the original dose escalation protocol, subjects in the febuxostat 40 mg group, who initially received 10 mg/day of febuxostat for 2 weeks (for 12 days in Study TMX-67-[redacted]) and then 40 mg/day of febuxostat, tended to experience gouty arthritis including those for which a causal relationship to the study drug could not be ruled out more frequently than subjects in the placebo and allopurinol groups.

Consequently, PMDA has concluded that the risk of gouty arthritis associated with febuxostat administered based on the new dose escalation protocol selected with the aim of reducing the incidence of gouty arthritis commonly found early during therapy is acceptable, but that the applicant should provide an appropriate precautionary statement regarding handling of gouty arthritis on treatment with febuxostat and continue to collect information on occurrence of gouty arthritis by post-marketing surveillance.

4.(iii).B.(3).2) Kidney/bladder-related adverse events

The major kidney/bladder-related adverse event reported in the 5 Japanese clinical studies was urinary β_2-MG increased, the incidence of which in individual studies is shown in Table 29. The incidence of urinary β_2-MG increased in the 2 Japanese long-term treatment studies was 4.7% (8 of 171) of subjects in the 28-week treatment group and 9.1% (12 of 132) of subjects in the 52-week treatment group in Study TMX-67-[redacted]; and 6.9% (9 of 131) of subjects in the febuxostat 40 mg group and 5.0% (2 of 40) of subjects in the febuxostat 60 mg group in Study TMX-67-[redacted].

Table 29. Incidence of urinary β_2-MG increased in the 5 Japanese clinical studies

Treatment group	TMX-67-[redacted] (8-week treatment)	TMX-67-[redacted] (8-week treatment)	TMX-67-[redacted] (8-week treatment)	TMX-67-[redacted] (16-week treatment)	TMX-67-[redacted] (16-week treatment)
Placebo	3/28 (10.7)	-	3/33 (9.1)	0/38 (0.0)	-
Febuxostat 10 mg	1/29 (3.4)	-	-	-	-
Febuxostat 20 mg	6/29 (20.7)	-	3/35 (8.6)	2/43 (4.7)	-
Febuxostat 40 mg	2/31 (6.5)	8/122 (6.6)	3/34 (8.8)	1/41 (2.4)	3/10 (30.0)
Febuxostat 60 mg	-	-	-	1/36 (2.8)	1/10 (10.0)
Febuxostat 80 mg	-	-	-	0/41 (0.0)	-
Allopurinol	-	7/121 (5.8)	-	-	2/20 (10.0)

Number of subjects who experienced the event/number of subjects analyzed (incidence, %)

Severe kidney/bladder-related adverse events were not reported in any of the 5 Japanese clinical studies or the 2 Japanese long-term treatment studies; moderate kidney/bladder-related adverse events included calculus ureteric (1 subject in the febuxostat 40 mg group in Study TMX-67-[redacted]), calculus urinary (1 subject each in the 28- and 52-week treatment groups in Study TMX-67-[redacted]), oedema peripheral (1 subject each in the 52-week treatment group in Study TMX-67-[redacted] and the febuxostat 40 and 60 mg groups in Study TMX-67-[redacted]), blood urine present (1 subject in the 52-week treatment group in Study TMX-67-[redacted]), and white blood cells urine positive (1 subject in the 28-week treatment group in Study TMX-67-[redacted]); and all the other kidney/bladder-related adverse events were mild in severity. Kidney/bladder-related adverse events that were assessed to be adverse drug reactions included urinary β_2-MG increased (1 subject each in the 52-week treatment group in Study TMX-67-[redacted], the allopurinol group in Study TMX-67-[redacted], the febuxostat 20 and 40 mg groups in Study TMX-67-[redacted], the febuxostat 40 and 60 mg and allopurinol groups in Study TMX-67-[redacted], and the febuxostat 40 mg group in Study TMX-67-[redacted]), blood creatinine increased (1 subject each in the 28-week treatment group in Study TMX-67-[redacted] and the febuxostat 40 mg group in Study TMX-67-[redacted]), blood urea increased (1 subject in the febuxostat 40 mg group in Study TMX-67-[redacted]), blood urine present (1 subject each in the placebo group in Study TMX-67-[redacted] and the febuxostat 40 mg group in Study TMX-67-[redacted]), protein urine present (1 subject each in the allopurinol group in Study TMX-67-[redacted] and the febuxostat 40 mg group in Study TMX-67-[redacted]), and renal function test abnormal (1 subject in the febuxostat 60 mg group in Study TMX-67-[redacted]), for all of which severity were mild. No findings suggested xanthine calculi.

PMDA asked the applicant to explain the effects of febuxostat on renal function.

The applicant's response:
Evaluation of the change in eGFR[51] over time after dosing by baseline eGFR based on the data of the 5 Japanese clinical studies and the 2 Japanese long-term treatment studies (Figures 5 to 7) revealed no tendency for the eGFR values to decrease over time.

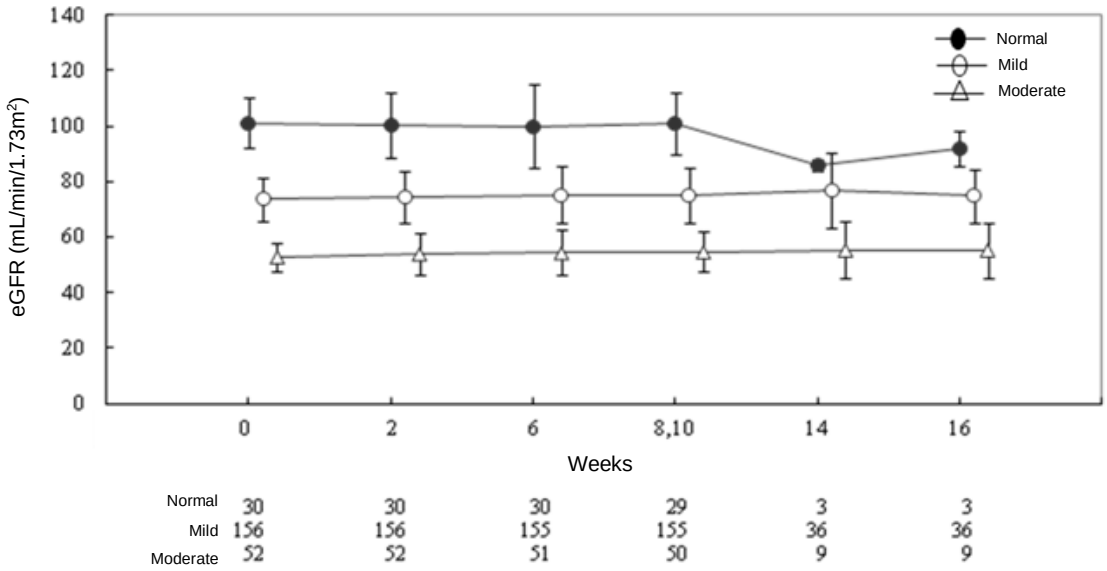

Figure 5. Change in eGFR (mean ± SD) over time after dosing in the 5 Japanese clinical studies by baseline eGFR (febuxostat 40 mg group)

[51] Renal function was defined as follows: normal, eGFR ≥90 mL/min; mild impairment, eGFR ≥60 to <90 mL/min; moderate impairment, eGFR ≥30 to <60 mL/min; and severe impairment, eGFR <30 mL/min.

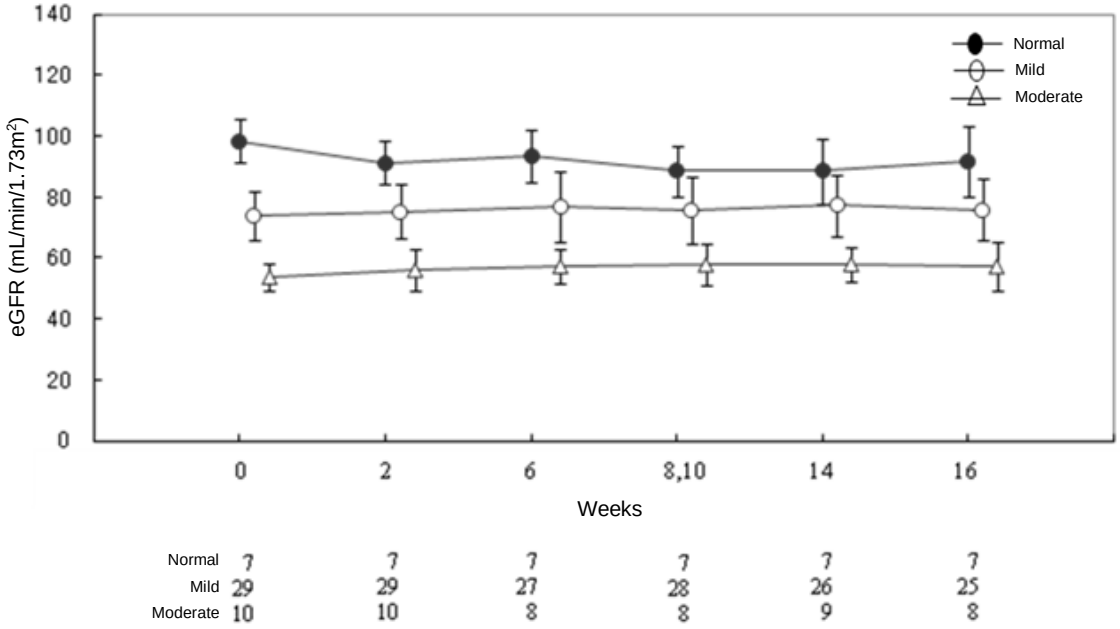

Figure 6. Change in eGFR (mean ± SD) over time after dosing in the 5 Japanese clinical studies by baseline eGFR (febuxostat 60 mg group)

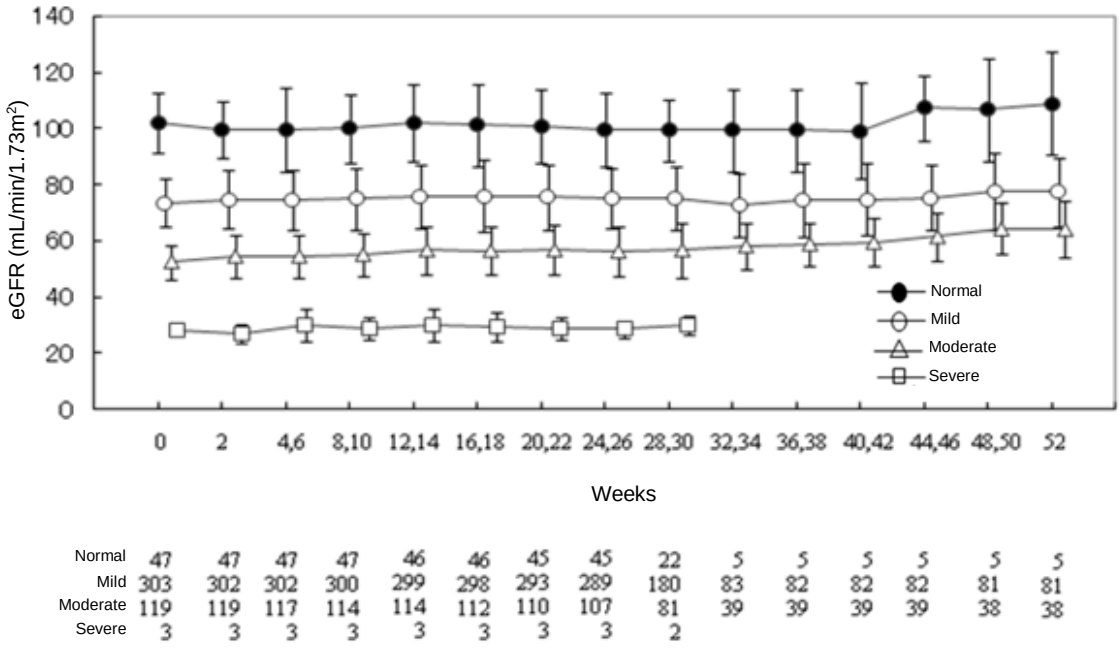

Figure 7. Change in eGFR (mean ± SD) over time after dosing in the 2 Japanese long-term treatment studies by baseline eGFR

PMDA has concluded that febuxostat is unlikely to significantly affect renal function because there was no tendency for the incidence of urinary β_2-MG increased to be consistently higher in the febuxostat group than in the placebo or allopurinol group in the 5 Japanese clinical studies and the observed urinary β_2-MG increased were mild in severity, and because decrease in the eGFR levels was not observed after dosing in the 5 Japanese clinical studies and the 2 Japanese long-term treatment studies.

4.(iii).B.(3).3) Thyroid function-related adverse events

The major thyroid function-related adverse event reported in the 5 Japanese clinical studies was blood TSH increased, the incidence of which in individual studies is shown in Table 30. The incidence of blood TSH increased in the 2 Japanese long-term treatment studies was 2.9% (5 of 171) of subjects in the 28-week treatment group and 3.8% (5 of 132) of subjects in the 52-week treatment group in Study TMX-67-[redacted]; and 0.8% (1 of 131) of subjects in the febuxostat 40 mg group and 0.0% (0 of 40) of

subjects in the febuxostat 60 mg group in Study TMX-67-[redacted].

Table 30. Incidence of blood TSH increased in the 5 Japanese clinical studies

Treatment group	TMX-67-[redacted] (8-week treatment)	TMX-67-[redacted] (8-week treatment)	TMX-67-[redacted] (8-week treatment)	TMX-67-[redacted] (16-week treatment)	TMX-67-[redacted] (16-week treatment)
Placebo	1/28 (3.6)	-	1/33 (3.0)	0/38 (0.0)	-
Febuxostat 10 mg	1/29 (3.4)	-	-	-	-
Febuxostat 20 mg	0/29 (0.0)	-	2/35 (5.7)	1/43 (2.3)	-
Febuxostat 40 mg	1/31 (3.2)	3/122 (2.5)	2/34 (5.9)	2/41 (4.9)	1/10 (10.0)
Febuxostat 60 mg	-	-	-	0/36 (0.0)	0/10 (0.0)
Febuxostat 80 mg	-	-	-	0/41 (0.0)	-
Allopurinol	-	1/121 (0.8)	-	-	0/20 (0.0)

Number of subjects who experienced the event/number of subjects analyzed (incidence, %)

Blood TSH increased that were assessed to be adverse drug reactions included those reported by 1 subject in the febuxostat 10 mg group in Study TMX-67-[redacted], 1 subject each in the febuxostat 40 mg and allopurinol groups in Study TMX-67-[redacted], 1 subject in the febuxostat 40 mg group in Study TMX-67-[redacted], 2 subjects in the febuxostat 40 mg group in Study TMX-67-[redacted], and 1 subject in the febuxostat 40 mg group in Study TMX-67-[redacted]. In addition, blood TSH increased that were assessed to be adverse drug reactions were reported by 2 subjects in the 28-week treatment group in Study TMX-67-[redacted] and 1 subject in the febuxostat 40 mg group in Study TMX-67-[redacted].

PMDA's view:
Given the facts that (i) the mechanism of the decrease in thyroid hormone in rodents is unclear, (ii) the incidence of blood TSH increased was higher in the febuxostat group than in the placebo and allopurinol groups despite no decreases in free T_3 and T_4 in the 5 Japanese clinical studies and the 2 Japanese long-term treatment studies, and (iii) hypothyroidism was reported in foreign long-term treatment studies (Studies TMX-[redacted]-05 and C02-021, reference data), a precautionary statement should be provided so that patients receiving febuxostat should be monitored for thyroid-related signs and if any abnormalities are observed, patients should be examined for thyroid function. In addition, information on occurrence of thyroid function-related adverse events should continue to be collected by post-marketing surveillance.

4.(iii).B.(3).4) Liver function-related adverse events

The major liver function-related adverse events reported in the 5 Japanese clinical studies were ALT increased, AST increased, and γ-GTP increased, the incidence of which in individual studies is shown in Table 31. The incidence of ALT increased in the 2 Japanese long-term treatment studies was 9.9% (17 of 171) of subjects in the 28-week treatment group and 14.4% (19 of 132) of subjects in the 52-week treatment group in Study TMX-67-[redacted]; and 1.5% (2 of 131) of subjects in the febuxostat 40 mg group and 0.0% (0 of 40) of subjects in the febuxostat 60 mg group in Study TMX-67-[redacted]. The incidence of AST increased was 7.0% (12 of 171) of subjects in the 28-week treatment group and 9.8% (13 of 132) of subjects in the 52-week treatment group in Study TMX-67-[redacted]; and 3.1% (4 of 131) of subjects in the febuxostat 40 mg group and 0.0% (0 of 40) of subjects in the febuxostat 60 mg group in Study TMX-67-[redacted]. The incidence of γ-GTP increased was 10.5% (18 of 171) of subjects in the 28-week treatment group and 16.7% (22 of 132) of subjects in the 52-week treatment group in Study TMX-67-[redacted]; and 5.3% (7 of 131) of subjects in the febuxostat 40 mg group and 2.5% (1 of 40) of subjects in the febuxostat 60 mg group in Study TMX-67-[redacted]. Subjects withdrawn from Study TMX-67-[redacted] were as follows: 1 subject who experienced ALT increased/AST increased in the 28-week treatment group; 1 subject who experienced ALT increased/AST increased (both were adverse drug reactions) and 1 subject who experienced ALT increased/AST increased/γ-GTP increased in the 52-week treatment group.

Table 31. Incidence of major liver function-related adverse events in the 5 Japanese clinical studies

Treatment group	TMX-67-[redacted] (8-week treatment)	TMX-67-[redacted] (8-week treatment)	TMX-67-[redacted] (8-week treatment)	TMX-67-[redacted] (16-week treatment)	TMX-67-[redacted] (16-week treatment)
ALT increased					
Placebo	2/28 (7.1)	-	4/33 (12.1)	1/38 (2.6)	-
Febuxostat 10 mg	2/29 (6.9)	-	-	-	-
Febuxostat 20 mg	4/29 (13.8)	-	3/35 (8.6)	1/43 (2.3)	-
Febuxostat 40 mg	2/31 (6.5)	4/122 (3.3)	2/34 (5.9)	0/41 (0.0)	0/10 (0.0)
Febuxostat 60 mg	-	-	-	1/36 (2.8)	1/10 (10.0)
Febuxostat 80 mg	-	-	-	2/41 (4.9)	-
Allopurinol	-	4/121 (3.3)	-	-	2/20 (10.0)
AST increased					
Placebo	2/28 (7.1)	-	2/33 (6.1)	1/38 (2.6)	-
Febuxostat 10 mg	1/29 (3.4)	-	-	-	-
Febuxostat 20 mg	2/29 (6.9)	-	2/35 (5.7)	1/43 (2.3)	-
Febuxostat 40 mg	0/31 (0.0)	3/122 (2.5)	3/34 (8.8)	0/41 (0.0)	0/10 (0.0)
Febuxostat 60 mg	-	-	-	0/36 (0.0)	0/10 (0.0)
Febuxostat 80 mg	-	-	-	0/41 (0.0)	-
Allopurinol	-	7/121 (5.8)	-	-	2/20 (10.0)
γ-GTP increased					
Placebo	1/28 (3.6)	-	3/33 (9.1)	0/38 (0.0)	-
Febuxostat 10 mg	1/29 (3.4)	-	-	-	-
Febuxostat 20 mg	4/29 (13.8)	-	4/35 (11.4)	2/43 (4.7)	-
Febuxostat 40 mg	2/31 (6.5)	3/122 (2.5)	1/34 (2.9)	1/41 (2.4)	0/10 (0.0)
Febuxostat 60 mg	-	-	-	1/36 (2.8)	0/10 (0.0)
Febuxostat 80 mg	-	-	-	1/41 (2.4)	-
Allopurinol	-	5/121 (4.1)	-	-	3/20 (15.0)

Number of subjects who experienced the event/number of subjects analyzed (incidence, %)

ALT increased and γ-GTP increased (both were adverse drug reactions) reported by 1 subject in the febuxostat 40 mg group in Study TMX-67-[redacted] were both severe, and resulted in study discontinuation. ALT increased, AST increased, and γ-GTP increased (all were adverse drug reactions) reported by 1 subject in the febuxostat 20 mg group in Study TMX-67-[redacted] were all of moderate severity, and resulted in study discontinuation.

PMDA's view:
There was no tendency for the incidence of liver function-related adverse events to be consistently higher in the febuxostat group than in the placebo or allopurinol group. However, since (i) some subjects were withdrawn from the study due to elevated liver-enzyme levels for which a causal relationship to febuxostat could not be ruled out in the 5 Japanese clinical studies and the 2 Japanese long-term treatment studies, and (ii) periodic liver function tests are recommended in the package insert for febuxostat overseas, a precautionary statement should be provided also in the Japanese package insert to ensure periodic liver function tests and information on occurrence of liver function-related adverse events should continue to be collected by post-marketing surveillance.

4.(iii).B.(3).5) Skin-related adverse events
PMDA conducted a review on skin-related adverse events because the clearance of radioactivity from the skin was delayed in the tissue distribution study of ^{14}C-febuxostat in rats and because non-clinical phototoxicity studies were not conducted despite the presence of UV absorption by febuxostat. The incidence of adverse events classified under the MedDRA System Organ Class "skin and subcutaneous tissue disorders" in the 5 Japanese clinical studies is shown in Table 32.

Table 32. Incidence of adverse events classified as "skin and subcutaneous tissue disorders" in the 5 Japanese clinical studies

Treatment group	TMX-67-[redacted] (8-week treatment)	TMX-67-[redacted] (8-week treatment)	TMX-67-[redacted] (8-week treatment)	TMX-67-[redacted] (16-week treatment)	TMX-67-[redacted] (16-week treatment)
Placebo	0/28 (0.0)	-	0/33 (0.0)	1/38 (2.6)	-
Febuxostat 10 mg	1/29 (3.4)	-	-	-	-
Febuxostat 20 mg	0/29 (0.0)	-	1/35 (2.9)	3/43 (7.0)	-
Febuxostat 40 mg	0/31 (0.0)	7/122 (5.7)	1/34 (2.9)	0/41 (0.0)	0/10 (0.0)
Febuxostat 60 mg	-	-	-	2/36 (5.6)	0/10 (0.0)
Febuxostat 80 mg	-	-	-	1/41 (2.4)	-
Allopurinol	-	6/121 (5.0)	-	-	0/20 (0.0)

Number of subjects who experienced the events/number of subjects analyzed (incidence, %)

Pruritus, rash, papule, and skin exfoliation reported by 4 subjects in the allopurinol group in Study TMX-67-[redacted], and rash reported by 1 subject in the febuxostat 20 mg group in Study TMX-67-[redacted] were assessed to be adverse drug reactions, and these rash in both studies were severe and resulted in withdrawal of the subjects. In the 2 Japanese long-term treatment studies, adverse drug reactions of rash and rash generalised reported by 1 subject each led to study discontinuation. No events of photosensitivity reaction were reported in the 5 Japanese clinical studies and the 2 Japanese long-term treatment studies.

PMDA's view:
Serious skin-related adverse events were not reported in Japanese clinical studies including photosensitivity reaction. However, given the facts that (i) rash (2 subjects) and rash generalised (1 subject) were reported as severe adverse drug reactions leading to study discontinuation, (ii) serious adverse drug reactions of Stevens-Johnson syndrome (2 subjects) were reported in the fourth periodic safety update reports (October 21, 2009 to April 20, 2010), and (iii) anaphylactic reaction and vasculitis possibly associated with the Stevens-Johnson syndrome were also reported as serious adverse drug reactions, precautionary statements should be included in the package insert. In addition, 1 subject in a foreign long-term treatment study (Study C02-021, reference data) experienced photosensitivity reaction of mild severity for which a causal relationship to febuxostat could not be ruled out. Therefore, information on occurrence of skin-related adverse events including photosensitivity reaction should continue to be collected by post-marketing surveillance.

4.(iii).B.(3).6) Cardiovascular adverse events

The incidence of cardiovascular adverse events in the pooled data from the 5 Japanese clinical studies and from the 2 Japanese long-term treatment studies is shown in Table 33.

Table 33. Incidence of cardiovascular adverse events

Adverse event	5 Japanese clinical studies			2 Japanese long-term treatment studies
	Placebo (N = 99)	Febuxostat (N = 461)	Allopurinol (N = 141)	Febuxostat (N = 474)
Cerebral infarction	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Carotid artery stenosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Putamen haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Atrial fibrillation	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Supraventricular extrasystoles	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Ventricular extrasystoles	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Arrhythmia	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)
Bradycardia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Hypertrophic cardiomyopathy	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Mitral valve incompetence	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Palpitations	0 (0.0)	0 (0.0)	0 (0.0)	7 (1.5)
Tachycardia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Left ventricular hypertrophy	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)
Chest discomfort	0 (0.0)	2 (0.4)	0 (0.0)	4 (0.8)
Chest pain	0 (0.0)	2 (0.4)	0 (0.0)	8 (1.7)
Blood pressure increased	1 (1.0)	3 (0.7)	3 (2.1)	4 (0.8)
Blood pressure systolic increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Electrocardiogram abnormal	0 (0.0)	3 (0.7)	3 (2.1)	7 (1.5)
Electrocardiogram QT prolonged	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Heart rate decreased	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Heart rate increased	0 (0.0)	0 (0.0)	1 (0.7)	3 (0.6)
Electrocardiogram T wave abnormal	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)

Number of subjects who experienced the event (incidence, %)

Although table 33 shows that there was no trend towards a particularly higher incidence of cardiovascular adverse events in the febuxostat group than that in the placebo or allopurinol group, this result was based on a limited number of subjects. PMDA asked the applicant to explain the responses to instructions regarding cardiovascular risk given by FDA and the European Medicines Agency (EMA).

The applicant's response:

(a) Responses to instructions in the U.S.

Instructions given by FDA and responses to the instructions made by TPNA (after marketing application in December 2004) are described below.

Because of concerns found during the regulatory review about the suggested trend towards a higher incidence of cardiovascular adverse events in the febuxostat group, FDA requested TPNA in [redacted] 20[redacted] to reevaluate the safety profile of febuxostat, especially the occurrence of cardiovascular adverse events by conducting an additional parallel-group comparative study or reanalyzing the currently available data. TPNA conducted a reanalysis of cardiovascular adverse events in [redacted] 20[redacted] based on the data from phase III randomized comparative studies (Studies C02-009 and C[redacted]-010) and newly obtained data from ongoing long-term extension studies (Studies TMX-[redacted]-005 and C02-021). For the purpose of the reanalysis, cardiovascular adverse events were identified using MedDRA preferred terms meeting criteria developed according to the Antiplatelet Trialists' Collaboration[52] (APTC) criteria. In addition, cardiovascular adverse events were re-identified from among all serious adverse events by cardiologists blinded to treatment assignment. As a result, TPNA determined that the risk of cardiovascular adverse events was comparable between the febuxostat and control groups. However, FDA concluded that the determination made by TPNA is equivocal because the number of subjects with cardiovascular adverse events was limited, no dose response relationships were observed, risk estimation was not accurate due to the limited number of subjects in the active control (allopurinol) group in the long-term extension studies, and the APTC criteria was used in the post hoc analyses. Subsequently, in [redacted] 20[redacted], FDA requested TPNA to provide, prior to approval, further data to clarify the cardiovascular risk of the proposed doses and/or provide data on the efficacy and safety of lower

[52] An international collaborative research organization that was established to identify the possible preventive effect of antiplatelet therapy against recurrent myocardial or cerebral infarction through meta-analysis of randomized comparative studies of antiplatelet therapy

doses of febuxostat with favorable risk-benefit characteristics, recommending that a repeat study with an adequate sample size be conducted to evaluate the risk of cardiovascular adverse events as well as to conduct a controlled trial to evaluate the efficacy and safety of lower doses of febuxostat. TPNA, receiving counseling from FDA, planned a randomized, double-blind, parallel-group comparative study (Study F-GT06-153) to evaluate the efficacy and safety of febuxostat versus allopurinol (200/300 mg) and conducted the study (from [redacted] 20[redacted] to [redacted] 20[redacted]). The results showed that not only the lower incidence of cardiovascular/thromboembolic adverse events but also the lower numbers of investigator-reported primary and secondary APTC adverse events[53] as well as of APTC adverse events adjudicated by the cardiovascular event committee[54] in the febuxostat group than those in the allopurinol group. Consequently, TPNA submitted an amendment application including the reanalysis results of the above and further data from the ongoing long-term extension study. Then, according to the requirements under the FDA Amendments Act of 2007 (FDAAA) for New Chemical Entities (NCEs), FDA requested a meeting of the Arthritis Advisory Committee (AAC) consisting of external experts in order to determine the cardiovascular safety profile of febuxostat and to define a dose level(s) with favorable risk-benefit balance. Prior to holding an AAC meeting, FDA concluded that no additional studies are needed because the analysis results provided by TPNA did not suggest a higher incidence of cardiovascular adverse events associated with febuxostat than with allopurinol. An AAC meeting held in November 2008 agreed that the benefits of febuxostat outweigh the risks and that febuxostat may be approved. After the above described processes, FDA issued an Approval Letter in February 2009, along with a request to include cardiovascular safety information in the labeling and to conduct a randomized parallel-group comparative study in an adequate sample size and follow-up duration to evaluate the incidence of serious cardiovascular adverse events associated with febuxostat versus allopurinol after the market launch. TPNA initiated a post-marketing clinical study (Study TMX-67_301) under the protocol agreed upon by FDA, which is now ongoing.

(b) Responses to instructions in Europe

Instructions given by EMA and responses to the instructions made by Ipsen (after marketing application via centralized procedure in August 2006) are described below.

The Committee for Medicinal Products for Human Use (CHMP) requested Ipsen to evaluate dose dependency of APTC events and to define patients at increased risk for the following reasons: (i) phase III studies (Studies C02-009 and C[redacted]-010) showed a trend towards higher incidence (0.8% in the febuxostat group, 0.2% in the allopurinol group) and rate per 100 patient-years of exposure (1.4 and 0.7, respectively) of primary APTC events (composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal heart attack, or non-fatal cardiac arrest) and (ii) long-term extension studies (Studies TMX-[redacted]-005 and C02-021) showed a trend towards higher incidence (2.64% [80 and 120 mg groups combined] and 0.56%, respectively) and rate per 100 patient-years of exposure (1.4 and 0.7, respectively) of primary APTC events in the febuxostat group than in the allopurinol group. Ipsen conducted an evaluation of the phase III study data to compare between the febuxostat and allopurinol groups, and determined that the numerical increase in the incidence of APTC events was an incidental finding based on the lack of significant difference in the incidence of APTC events, but responded that monitoring of cardiovascular adverse events will be conducted after the market launch to confirm that the incidence is within the range expected for gout patients in clinical settings. CHMP requested Ipsen to further explore strategies to minimize the risk of cardiovascular adverse events in gout patients receiving febuxostat, and to conduct a carefully designed prospective controlled cohort study in patients who received febuxostat or allopurinol to collect and analyze data on severity of gout, risk factors, and adverse event outcomes. Ipsen responded that Special Warnings and Precautions for Use regarding cardiovascular safety will be included in the Summary of Product Characteristics along with complementary education materials, and that an additional clinical study to evaluate cardiovascular risk will be conducted. After a series of discussions on the additional clinical study, marketing approval was granted in April 2008 (the marketing authorization for febuxostat was transferred from Ipsen to Menarini in [redacted] 20[redacted]). As a condition for the approval, an additional post-marketing safety study (Follow-Up Measure [FUM] 005: a phase IV, prospective, randomized, open-label, comparative cardiovascular safety study in patients

[53] Primary APTC adverse events consist of death due to cardiovascular adverse events, non-fatal myocardial infarction, non-fatal stroke, or non-fatal cardiac arrest. Secondary APTC adverse events consist of angina, coronary revascularisation, transient ischemic attack, venous and peripheral arterial vascular thrombotic events.

[54] Consisting of 3 independent cardiologists

receiving febuxostat or allopurinol) was required to evaluate cardiovascular safety, the protocol of which is now under discussion.

PMDA's view:
There are limitations in the evaluation of cardiovascular risk in Japanese patients receiving febuxostat because (i) the Japanese clinical study data on the incidence of cardiovascular adverse events (Table 33) were obtained based on a limited number of subjects although the data suggested no trend towards a particularly higher incidence in the febuxostat group than that in the placebo or allopurinol group, and (ii) short treatment durations (8 or 16 weeks) were used in the 5 Japanese clinical studies. In addition, the *Japanese Treatment Guideline* 2nd ed. states that elevated serum urate levels have been reported to correlate with an independent cardiovascular risk while it also states that changes in serum urate levels have been reported to be a sheer consequence of cardiovascular risk factors; thus, the degree of elevation of cardiovascular risk in patients with hyperuricemia and its ethnic differences do not seem to have been elucidated at present. Based on the above, close attention should be paid to foreign post-marketing safety data of febuxostat and data from ongoing foreign post-marketing clinical studies evaluating cardiovascular risk associated with febuxostat, and information on cardiovascular adverse events should continue to be collected by Japanese post-marketing surveillance planned to generate data allowing for comparison with foreign data. The above issues will be finalized, also taking account of comments raised in the Expert Discussion.

4.(iii).B.(4) Indication
PMDA asked the applicant to explain in detail the appropriateness of the proposed indication for febuxostat ("Amelioration of hyperuricemia in the following diseases: gout and hyperuricemia") in view of the difference from indication for febuxostat or approved drugs in the same class established in foreign countries, and of currently available scientific findings.

The applicant's response:
Different indications have been established for allopurinol in different countries, and each process of their approval is unclear. In the U.S. and U.K., allopurinol is indicated for gout only, while in Germany, France, Italy, and South Korea, allopurinol is indicated also for hyperuricemia in addition to gout. Based on the IMS's statistical survey on prescription, allopurinol has been mostly prescribed for gout patients in the U.S. and U.K., while it has been prescribed for patients with hyperuricemia approximately [redacted] to [redacted] times ([redacted]%-[redacted]%) more frequently than for gout patients in Germany, France, and Italy, presumably reflecting the difference in indication. Also in Japan, prescriptions of allopurinol and benzbromarone for patients with hyperuricemia have accounted for approximately [redacted]% of their overall prescriptions, and allopurinol has been prescribed for patients with hyperuricemia as much as [redacted] times ([redacted]%) more frequently than for gout patients. Thus, both in Japan and Europe, urate-lowering agents are widely used for treatment of hyperuricemia, and a certain level of consensus seems to have been reached on the need for treatment of hyperuricemia.

In the U.S., Europe, and South Korea, febuxostat is indicated only for gout due to the fact that the indication was determined based on the results of clinical studies conducted exclusively in gout patients in the U.S. In Japan, a 7-year survey measured serum urate in 48,177 male and female adults and revealed that the rate of transition to end-stage renal disease was approximately 6-fold higher among patients with hyperuricemia than among patients with normal serum urate levels (Kunitoshi I, et al., *Am J Kidney Dis.* 2004;44:642-650). Urate crystals have been found in synovial fluid of the metatarsophalangeal joint of patients with hyperuricemia (Rouault T, et al., *Arthritis Rheum.* 1982;25:209-212), and it has also been reported that urate deposition in the tendon, synovium, and soft tissues in the knee and/or ankle is found in one third of patients with hyperuricemia and signs of inflammation are found in one fourth of patients with hyperuricemia (Puig JG, et al., *Nucleosides Nucleotides & Nucleic Acids.* 2008;27:592-595). Given these reports, urate deposition appears to steadily progress leading to an associated inflammation in a fair proportion of patients with hyperuricemia having no history of gout. In addition, some Japanese guidelines recommend the following: the Japanese Society of Nephrology eds. *Clinical Practice Guidebook for Diagnosis and Treatment of Chronic Kidney Disease* 2009. recommends that hyperuricemia be treated even in the absence of gouty arthritis because hyperuricemia is a risk factor for renal impairment; the *Japanese Treatment Guideline* 2nd ed. recommends that hyperuricemia be treated with urate-lowering agents for prevention of gouty arthritis because hyperuricemia is a primary disease of urate deposition diseases,

which are characterized by urate crystallization/deposition in body tissues such as joints and the kidney, and because incidence of gouty arthritis significantly increases with increasing blood urate levels (Hall AP, et al., *Am J Med.* 1967;42:27-37, Campion EW, et al., *Am J Med.* 1987;82:421-426, Lin KC, et al., *J Rheumatol.* 2000;27:1501-1505).

Consequently, it is appropriate to include hyperuricemia in the proposed indication for febuxostat in light of currently available scientific findings and treatment experiences.

PMDA's view:
At present, no worldwide consensus has been reached on the need for or significance of treatment of hyperuricemia without gouty arthritis or tophi. However, in clinical settings in Europe (excluding the U.K.) and Japan, it is evidenced that there is a certain level of the need for or significance of treatment of hyperuricemia because allopurinol, which is an approved drug with extensive clinical use in and out of Japan and is of the same class as the one febuxostat belongs to, has been prescribed for patients with hyperuricemia more frequently than for gout patients. In the U.S., Europe, and South Korea, febuxostat is indicated only for gout based on the results of clinical studies conducted exclusively in gout patients in the U.S., while Japanese clinical studies of febuxostat were conducted in patients with hyperuricemia including gout and demonstrated the efficacy of febuxostat [see "4.(iii).B.(2) Efficacy"]. Given the above points and the descriptions regarding therapeutic indications of urate-lowering agents found in the *Japanese Treatment Guideline* 2nd ed., there is no significant problem with including patients with serum urate levels ≥8.0 mg/dL who have renal impairment (including urinary calculus) or complications such as hypertension, ischemic heart disease, and diabetes mellitus, which are potential risk factors for cardiovascular disorders, and patients with serum urate levels ≥9.0 mg/dL even after lifestyle modifications in the intended population for febuxostat in addition to gout patients. The indication should be modified to reflect the above intended patient population, and appropriate descriptions should be included in the Precautions for Indications section of the package insert. These issues will be finalized, also taking account of comments raised in the Expert Discussion.

4.(iii).B.(5) Dosage and administration
The applicant explained as follows:
4.(iii).B.(5).1) Dose regimen
A multiple-dose study in healthy adult male subjects (Study TMX-67-[redacted]) indicated that an adequate blood urate lowering activity can be achieved by once-daily administration of febuxostat. Because once-daily administration is preferable also from a viewpoint of convenience of medication, phase II and III studies used such dosing regimen for efficacy and safety evaluation. In addition, a supplemental multiple-dose study in healthy adult male subjects (Study TMX-67-[redacted]) evaluated the blood urate lowering activity of febuxostat administered in once-daily versus twice-daily dosing regimens. The results showed that an adequate blood urate lowering activity can be achieved by the once-daily regimen, although more potent effects can be obtained by the twice-daily regimen. The once-daily dosing regimen was considered preferable also for the purpose of reducing the risk of gouty arthritis early during therapy. Timing of dosing relative to meals was not specified in the application because phase I food effect studies (Studies TMX-67-[redacted] and -[redacted]) in healthy adult male subjects showed a 13% to 18% decrease in the AUC-based drug absorption but showed no effects on the blood urate lowering activity.

4.(iii).B.(5).2) Dose level
(a) Initial dose
Because a rapid fall in serum urate levels caused by a urate-lowering agent early during therapy has been known to frequently induce gouty arthritis, the *Japanese Treatment Guideline* 2nd ed. recommends that treatment with a urate-lowering agent be started at a low dose level (i.e., 1/3 to 1/2 times the usual dose). Since the effective dose of febuxostat was considered to be within the range of 20 to 40 mg/day based on the results from early phase II studies (Studies TMX-67-[redacted] and TMX-67-[redacted]), an initial dose level of 10 mg/day was selected for late phase II and later studies. In Studies TMX-67-[redacted], TMX-67-[redacted], TMX-67-[redacted], and TMX-67-[redacted], the incidence of gouty arthritis during treatment with 10 mg/day of febuxostat (0.6% [2 of 314 subjects]) was not substantially different from that during treatment with allopurinol at the initial dose (100 mg/day) (0.9% [1 of 106 subjects]), and was lower than that in the placebo group (3.2% [2 of 63 subjects]).

(b) Dose escalation regimen

The incidence of gouty arthritis was compared between the dose escalation regimens based on the data from Studies TMX-67-[redacted], TMX-67-[redacted], TMX-67-[redacted], and TMX-67-[redacted]. The results showed that the incidence with the 2-step dose escalation regimen (initial dose of 10 mg/day was increased to 20 mg/day, then to 40 mg/day) used in Studies TMX-67-[redacted] and TMX-67-[redacted] (6.5% [9 of 138 subjects]) was almost one half the incidence with the 1-step dose escalation regimen (initial dose of 10 mg/day was increased to 40 mg/day) used in Studies TMX-67-[redacted] and TMX-67-[redacted] (11.0% [12 of 109 subjects]), and was not substantially different from that in the placebo (7.9% [5 of 63 subjects]) or allopurinol (6.6% [7 of 106 subjects]) group. Based on the above results, a dose escalation regimen starting at 10 mg/day of febuxostat with gradual escalation was considered appropriate. The Precautions for Dosage and Administration section will state that febuxostat should be started at 10 mg once daily and the dose should be gradually increased while monitoring the patient's blood urate level because a rapid fall in blood urate levels may induce gouty arthritis (gout attack) during the early phase of treatment with a urate-lowering agent.

(c) Usual dose

Based on the pooled data from Japanese studies evaluating efficacy other than long-term treatment studies, the percentage of subjects who achieved serum urate levels ≤6.0 mg/dL was 24.1% (7 of 29 subjects) at 10 mg/day, 51.4% (55 of 107 subjects) at 20 mg/day, and 83.2% (198 of 238 subjects) at 40 mg/day, showing a dose-dependent increase. In particular, the percentage of subjects who achieved serum urate levels ≤6.0 mg/dL at Week 8 was significantly higher in the 40 mg/day group than in the allopurinol (200 mg/day) group (P = 0.034, Study TMX-67-[redacted]). At higher doses, the percentage was 84.4% (38 of 45 subjects) at 60 mg/day and 87.8% (36 of 41 subjects) at 80 mg/day, showing no substantial difference as compared with that in the 40 mg/day group. Thus, the usual dose of febuxostat was determined to be 40 mg/day.

(d) Maximum dose

As described in the above section, although febuxostat at >40 mg/day is not so much expected to increase the percentage of patients who can achieve serum urate levels ≤6.0 mg/dL, the pooled study data showed that the rate of change in serum urate level (mean ± SD) was -41.9% ± 12.6% at 40 mg/day, -49.2% ± 16.6% at 60 mg/day, and -52.0% ± 17.5% at 80 mg/day. In Study TMX-67-[redacted], among 32 subjects who did not achieve serum urate levels ≤6.0 mg/dL at Week 10 of treatment with 40 mg/day of febuxostat and then underwent a dose increase to 60 mg/day at ≥Week 15, 28 subjects (87.5%) achieved serum urate levels ≤6.0 mg/dL at Week 52. No substantial difference in the safety was seen between the 40 and 60 mg/day groups. Thus, the maximum dose level of febuxostat was determined to be 60 mg/day.

Given the fact that subjects who underwent a 1-step dose increase from 10 to 40 mg/day frequently experienced gouty arthritis in clinical studies including Study TMX-67-[redacted], PMDA asked the applicant to explain the appropriateness of descriptions in the Precautions for Dosage and Administration section of the package insert.

The applicant's response:

The description in the Precautions for Dosage and Administration section will be modified as shown below, taking into consideration the following treatment regimen recommended by the *Japanese Treatment Guideline* 2nd ed.: treatment with a urate-lowering agent should be started at a low dose level (i.e., 1/3 to 1/2 times the usual dose) followed by 3- to 6-month gradual dose escalation to determine the maintenance dose in order to reduce the risk of gouty arthritis early during therapy, while the patient's serum urate level is being monitored.

"Precautions for Dosage and Administration" (Underline denotes additions.)

A rapid fall in blood urate levels may induce gouty arthritis (gout attack) during the early phase of treatment with a urate-lowering agent. <u>The initial dose of febuxostat should be 10 mg once daily and the dose should be gradually increased (to 20 mg, and then to 40 mg)</u> while monitoring the patient's blood urate level.

PMDA's view:

In light of the efficacy and safety data from studies conducted based on the dose escalation protocol selected at the early developmental phase and studies conducted based on the new dose escalation protocol selected after withdrawal of regulatory application, there is no problem with the applicant's

view that febuxostat should be orally administered once daily at unspecified timing relative to meals with the initial, usual, and maximum dose levels being 10, 40, and 60 mg/day, respectively. However, PMDA has requested that the applicant take further measures against gouty arthritis because, in addition to specifying that the dose should be started at 10 mg/day and then be gradually increased in the "Dosage and Administration" section, a precautionary statement should include detailed description of the specific manner for dose escalation (dose levels and durations) up to the usual dose (40 mg/day) in the "Precautions for Dosage and Administration" section for the purpose of reducing the incidence of gouty arthritis caused by an abrupt reduction of serum urate levels. Specific descriptions in the "Dosage and Administration" and "Precautions for Dosage and Administration" sections will be finalized, taking account of comments raised in the Expert Discussion.

4.(iii).B.(6) Use in special populations

4.(iii).B.(6).1) Patients with renal impairment

The incidence of adverse events and adverse drug reactions (both including abnormal laboratory changes) reported in the 5 Japanese clinical studies and the 2 Japanese long-term treatment studies is shown by eGFR in Table 34.

Table 34. Incidence of adverse events and adverse drug reactions (both including abnormal changes in laboratory values) by baseline eGFR

		eGFR[a)]	5 Japanese clinical studies			2 Japanese long-term treatment studies
			Placebo	Febuxostat	Allopurinol	Febuxostat
Adverse event						
	Overall	Normal	8/11 (72.7)	44/62 (71.0)	18/22 (81.8)	44/47 (93.6)
		Mild	38/53 (71.7)	189/285 (66.3)	52/83 (62.7)	274/303 (90.4)
		Moderate	24/35 (68.6)	83/114 (72.8)	25/35 (71.4)	106/119 (89.1)
		Severe	-	-	1/1 (100.0)	3/3 (100.0)
	Gouty arthritis	Normal	1/11 (9.1)	7/62 (11.3)	1/22 (4.5)	13/47 (27.7)
		Mild	4/53 (7.5)	30/285 (10.5)	6/83 (7.2)	65/303 (21.5)
		Moderate	2/35 (5.7)	21/114 (18.4)	4/35 (11.4)	14/119 (11.8)
		Severe	-	-	0/1 (0.0)	0/3 (0.0)
Adverse drug reactions						
	Overall	Normal	2/11 (18.2)	12/62 (19.4)	5/22 (22.7)	17/47 (36.2)
		Mild	6/53 (11.3)	49/285 (17.2)	10/83 (12.0)	83/303 (27.4)
		Moderate	3/35 (8.6)	25/114 (21.9)	4/35 (11.4)	28/119 (23.5)
		Severe	-	-	0/1 (0.0)	2/3 (66.7)
	Gouty arthritis	Normal	0/11 (0.0)	4/62 (6.5)	1/22 (4.5)	10/47 (21.3)
		Mild	1/53 (1.9)	20/285 (7.0)	4/83 (4.8)	50/303 (16.5)
		Moderate	1/35 (2.9)	12/114 (10.5)	1/35 (2.9)	8/119 (6.7)
		Severe	-	-	0/1 (0.0)	0/3 (0.0)

Number of subjects who experienced the event/number of subjects analyzed (incidence, %); -, Not applicable

a) Renal function was defined as follows: normal, eGFR ≥90 mL/min; mild impairment, eGFR ≥60 to <90 mL/min; moderate impairment, eGFR ≥30 to <60 mL/min; and severe impairment, eGFR <30 mL/min.

The applicant's explanation:

After stratification by eGFR, the incidence of adverse drug reactions among subjects with normal renal function, subjects with mild renal impairment, and subjects with moderate renal impairment was 19.4% (12 of 62) of subjects, 17.2% (49 of 285) of subjects, and 21.9% (25 of 114) of subjects, respectively, in the 5 Japanese clinical studies, and 36.2% (17 of 47) of subjects, 27.4% (83 of 303) of subjects, and 23.5% (28 of 119) of subjects, respectively, in the 2 Japanese long-term treatment studies, showing no increase in the incidence with decreasing renal function. In addition, in Japanese clinical studies, an adequate efficacy was demonstrated as evidenced by the finding that the percentage of subjects who achieved serum urate levels ≤6.0 mg/dL was 60% to ≥70% both among subjects with normal renal function and among patients with mild to moderate renal impairment. C_{max} and $AUC_{0\text{-}24h}$ of unchanged febuxostat in patients with mild renal impairment were approximately 1.0- and 1.5-fold higher, and those in patients with moderate renal impairment were approximately 1.3- and 1.7-fold higher than those in subjects with normal renal function (Study TMX-67-[redacted]), but no notable differences in the safety and efficacy were seen in patients with renal impairment of moderate or lower severity; thus, there is no need for dose adjustment in patients with renal impairment of moderate or lower severity.

PMDA asked the applicant to explain the safety in patients with severe renal impairment including patients on dialysis.

The applicant's response:
There were only 3 patients with severe renal impairment who received febuxostat in Japanese clinical studies (all were participants in the 2 Japanese long-term treatment studies); these subjects experienced adverse events of oral herpes/hyperlipidaemia/vertigo/diarrhoea/vomiting/erythema/chest pain, nasopharyngitis/somnolence/peripheral coldness/rash/pruritus genital/constipation/contusion, and blood TSH increased. All these events were of moderate or lower severity. Of these, hyperlipidaemia, vertigo, and blood TSH increased were assessed to be adverse drug reactions. Patients on dialysis were not included in Japanese or foreign clinical studies of febuxostat, while in a foreign long-term treatment study (Study C02-021, reference data), 3 patients experienced renal failure (a causal relationship to the study drug was ruled out for all events) during the study period and underwent dialysis. Treatment with febuxostat at 80 mg/day was continued (for up to 153 days) after the initiation of dialysis. During treatment with febuxostat after dialysis was initiated, 1 of the 3 subject experienced severe renal failure and mild gastrooesophageal reflux disease, for which a causal relationship to febuxostat was ruled out; no adverse events were reported by the other 2 subjects. Clinical experience in 7 patients on dialysis has been reported from foreign post-marketing surveillance of febuxostat (the reported dose level of febuxostat was 40 or 80 mg/day, and the maximum duration of treatment was approximately 1 year). The 7 patients each reported 1 adverse event of the following: serious stroke, cessation of dialysis, fatal end-stage renal failure, blood creatinine increased, acute hepatic failure, or cardiac failure congestive/pneumonia; or non-serious headache. One patient each who experienced acute hepatic failure or headache, those for which a causal relationship to febuxostat could not be ruled out was withdrawn from treatment with febuxostat, resulting in reversal of liver function test values to normal range and resolution of headache. The patient who experienced cardiac failure congestive/pneumonia recovered after hospital admission due to these events, and then administration of febuxostat was continued. Based on the above, no adverse events of safety concern indicating the need for dose adjustment of febuxostat were reported by patients with severe renal impairment who participated in clinical studies conducted so far, however, the safety of febuxostat in patients with severe renal impairment including patients on dialysis has not been well established because accumulation of clinical experience is limited and little clinical experience has been gained from patients on dialysis. Therefore, data on the use in patients with severe renal impairment overseas should be continuously collected and investigated via Japanese post-marketing surveillance.

In light of the applicant's claim that there is no need for dose adjustment of febuxostat in patients with renal impairment of moderate or lower severity, PMDA reviewed the efficacy based on the data from Study TMX-67-[redacted], which was conducted in the largest number of evaluable subjects receiving clinical doses (40 and 60 mg) of febuxostat using the longest treatment duration among 3 studies conducted using the new dose escalation scheme (41 and 36 subjects received 40 mg and 60 mg, respectively, for 16 weeks in Study TMX-67-[redacted], 10 and 9 subjects received 40 mg and 60 mg, respectively, for 16 weeks in Study TMX-67-[redacted], and 129 and 40 subjects received 40 mg and 60 mg, respectively, for 52 weeks in Study TMX-67-[redacted]) (Table 35).

Table 35. Percentage of subjects who achieved serum urate levels ≤6.0 mg/dL and rate of change in serum urate level from baseline (Study TMX-67-[redacted], by baseline eGFR)

Treatment group	eGFR[a)]	Number of subjects	Serum urate level	
			Percentage (number) of subjects who achieved serum urate levels ≤6.0 mg/dL	rate of change (%)
Febuxostat 40 mg	Overall	129	84.5% (109)	-45.55 ± 12.18
	Normal	14	92.9% (13)	-41.74 ± 17.92
	Mild	89	80.9% (72)	-45.07 ± 11.49
	Moderate	25	92.0% (23)	-48.19 ± 8.96
	Severe	1	100.0% (1)	-75.27
Febuxostat 60 mg	Overall	40	85.0% (34)	-49.34 ± 11.02
	Normal	10	90.0% (9)	-47.47 ± 10.89
	Mild	26	84.6% (22)	-49.34 ± 10.99
	Moderate	4	75.0% (3)	-54.02 ± 13.24
	Severe	0	-	-

Mean ± SD

a) Renal function was defined as follows: normal, eGFR ≥90 mL/min; mild impairment, eGFR≥ 60 to <90 mL/min; moderate impairment, eGFR ≥30 to <60 mL/min; and severe impairment, eGFR <30 mL/min.

PMDA's view:

When reviewed based on Table 34, there would be no significant problems with the safety in patients with renal impairment of moderate or lower severity. However, a precautionary statement should be provided so that febuxostat should be administered carefully in patients with severe renal impairment and the safety in patients with renal impairment should be continuously investigated because the number of studied patients with severe renal impairment including patients on dialysis was very limited. When efficacy is reviewed based on Table 35, the presence of serum urate lowering effect in patients with renal impairment of moderate or lower severity receiving 40 mg and in patients with renal impairment of mild or lower severity receiving 60 mg of febuxostat should not be denied. However, because the numbers of studied patients with moderate renal impairment receiving 60 mg and patients with severe renal impairment receiving 40 or 60 mg of febuxostat were limited, the efficacy in patients with renal impairment including such patients should be continuously investigated. The data from Japanese clinical studies suggest no need for dose adjustment in patients with renal impairment, but it is appropriate to closely monitor the patient's condition and ensure an adequate dose escalation period when febuxostat is used in patients with severe renal impairment. Based on the above, information on the safety and efficacy in patients with renal impairment should continue to be collected by post-marketing surveillance.

4.(iii).B.(6).2) Patients with hepatic impairment

The incidence of adverse events and adverse drug reactions (both including abnormal laboratory changes) reported in the 5 Japanese clinical studies and the 2 Japanese long-term treatment studies is shown in Table 36 for patients with ALT or AST levels of more than the upper limit of normal (ULN) and the other patients separately.

Table 36. Incidence of adverse events and adverse drug reactions (both including abnormal changes in laboratory values) by baseline ALT or AST

		ALT or AST	5 Japanese clinical studies			2 Japanese long-term treatment studies
			Placebo	Febuxostat	Allopurinol	Febuxostat
Adverse event						
	Overall	> ULN	12/21 (57.1)	81/109 (74.3)	24/31 (77.4)	129/144 (89.6)
		≤ ULN	58/78 (74.4)	234/351 (66.7)	72/110 (65.5)	298/328 (90.9)
	ALT increased	> ULN	4/21 (19.0)	7/109 (6.4)	3/31 (9.7)	15/144 (10.4)
		≤ ULN	3/78 (3.8)	15/351 (4.3)	3/110 (2.7)	22/328 (6.7)
	AST increased	> ULN	4/21 (19.0)	5/109 (4.6)	5/31 (16.1)	12/144 (8.3)
		≤ ULN	1/78 (1.3)	7/351 (2.0)	4/110 (3.6)	16/328 (4.9)
	γ-GTP increased	> ULN	3/21 (14.3)	6/109 (5.5)	5/31 (16.1)	17/144 (11.8)
		≤ ULN	1/78 (1.3)	14/351 (4.0)	3/110 (2.7)	31/328 (9.5)
Adverse drug reactions						
	Overall	> ULN	3/21 (14.3)	21/109 (19.3)	5/31 (16.1)	40/144 (27.8)
		≤ ULN	8/78 (10.3)	64/351 (18.2)	14/110 (12.7)	90/328 (27.4)
	ALT increased	> ULN	1/21 (4.8)	4/109 (3.7)	0/31 (0.0)	2/144 (1.4)
		≤ ULN	0/78 (0.0)	2/351 (0.6)	1/110 (0.9)	9/328 (2.7)
	AST increased	> ULN	1/21 (4.8)	1/109 (0.9)	0/31 (0.0)	1/144 (0.7)
		≤ ULN	0/78 (0.0)	0/351 (0.0)	1/110 (0.9)	4/328 (1.2)
	γ-GTP increased	> ULN	0/21 (0.0)	2/109 (1.8)	1/31 (3.2)	2/144 (1.4)
		≤ ULN	0/78 (0.0)	0/351 (0.0)	1/110 (0.9)	9/328 (2.7)

Number of subjects who experienced the event/number of subjects analyzed (incidence, %)

PMDA asked the applicant to explain the safety in patients with severe hepatic impairment.

The applicant's response:
Since patients with hepatic impairment were excluded from the 5 Japanese clinical studies and the 2 Japanese long-term treatment studies, patients with severe hepatic impairment will be listed in the Careful Administration section of the draft package insert and a precautionary statement that the safety of febuxostat has not been established in patients with severe hepatic impairment will be provided.

PMDA's view:
Given that the 5 Japanese clinical studies and the 2 Japanese long-term treatment studies excluded patients with AST or ALT levels of >2 times the ULN, and that a precautionary statement should be provided to ensure periodic liver function tests during treatment with febuxostat [see "4.(iii).B.(3).4) Liver function-related adverse events"], not only patients with severe hepatic impairment but also patients with any hepatic impairment should be listed in the Careful Administration section of the package insert. In addition, information on the safety in patients with hepatic impairment should continue to be collected by post-marketing surveillance.

4.(iii).B.(6).3) Elderly patients and women

The incidence of adverse events and adverse drug reactions (both including abnormal laboratory changes) reported in the 5 Japanese clinical studies and the 2 Japanese long-term treatment studies is shown by age and sex in Table 37.

Table 37. Incidence of adverse events and adverse drug reactions (both including abnormal changes in laboratory values) by age and sex

	Age[a)] or sex	5 Japanese clinical studies			2 Japanese long-term treatment studies
		Placebo	Febuxostat	Allopurinol	Febuxostat
Overall adverse events	Non-elderly subjects	55/77 (71.4)	267/383 (69.7)	74/112 (66.1)	363/403 (90.1)
	Elderly subjects	15/22 (68.2)	49/78 (62.8)	22/29 (75.9)	66/71 (93.0)
	Male	68/97 (70.1)	311/453 (68.7)	94/138 (68.1)	415/460 (90.2)
	Female	2/2 (100.0)	5/8 (62.5)	2/3 (66.7)	14/14 (100.0)
Overall adverse drug reactions	Non-elderly subjects	8/77 (10.4)	71/383 (18.5)	13/112 (11.6)	108/403 (26.8)
	Elderly subjects	3/22 (13.6)	15/78 (19.2)	6/29 (20.7)	23/71 (32.4)
	Male	10/97 (10.3)	85/453 (18.8)	19/138 (13.8)	126/460 (27.4)
	Female	1/2 (50.0)	1/8 (12.5)	0/3 (0.0)	5/14 (35.7)

Number of subjects who experienced the event/number of subjects analyzed (incidence, %)
a) Non-elderly subjects are defined as subjects aged <65 years, and elderly subjects are defined as subjects aged ≥65 years.

The applicant's explanation:
No substantial difference in the incidence of adverse events or adverse drug reactions was found between elderly and non-elderly subjects in the 5 Japanese clinical studies. In these studies, major adverse events reported at a high incidence in elderly subjects receiving febuxostat included C-reactive protein (CRP) increased (12.8% [10 of 78 subjects]), nasopharyngitis (9.0%, [7 of 78 subjects]), gouty arthritis (7.7%, [6 of 78 subjects]), and diarrhoea, urinary β_2-MG increased, blood CK increased, and blood TSH increased (6.4% each, [5 of 78 subjects]). Among these, CRP increased, diarrhoea, and blood TSH increased were reported at a higher incidence in elderly subjects than in non-elderly subjects (the incidence of non-elderly subjects; 11.2% [43 of 383 subjects], 3.4% [13 of 383 subjects], and 2.1% [8 of 383 subjects], respectively). In the 2 Japanese long-term treatment studies, the incidence of adverse events and adverse drug reactions were slightly higher in elderly subjects. In the 2 studies, major adverse events reported at a high incidence in elderly subjects receiving febuxostat included gouty arthritis, pain in extremity, and γ-GTP increased (9.9% each, [7 of 71 subjects]). Evaluation of impact on the safety according to sex could not be performed because of the bias in the number of subjects: The numbers of male and female subjects were 453 and 8, respectively, in the 5 Japanese clinical studies, and 460 and 14, respectively, in the 2 Japanese long-term treatment studies.

PMDA's view:
A precautionary statement should be provided so that febuxostat should be carefully administered to elderly patients, who often have reduced physiological function and may suffer from rapid decline in renal function. Information on the safety in elderly patients and women should continue to be collected by post-marketing surveillance because clinical experience of febuxostat in female patients is limited.

4.(iii).B.(7) Post-marketing surveillance

The applicant plans to conduct a post-marketing surveillance in patients with gout and/or hyperuricemia to evaluate the long-term safety and efficacy of febuxostat (planned sample size, [redacted]; observation period, [redacted] years; survey period, [redacted] years).

PMDA's view:
PMDA has requested that the applicant further address this because the limited experience with febuxostat in clinical studies mandates continued collection of information on occurrence of gouty arthritis, adverse events related to thyroid function, liver function, or the cardiovascular system following treatment with febuxostat, and safety in patients with renal or hepatic impairment, elderly patients, and women by post-marketing surveillance. The above points, and particularly, the evaluation method of cardiovascular risk will be finalized, taking account of comments raised in the Expert Discussion.

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

Document-based compliance inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application.

As a result, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

2. PMDA's conclusion on the results of GCP on-site inspection

GCP on-site inspection was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.5.1-2, 5.3.5.1-5, and 5.3.5.2-2). As a result, cases of violation of inclusion criteria specified in the protocol and protocol deviations (local laboratory testing was performed that was prohibited in order to maintain blinding) were found at some clinical trial sites. In addition, the inspection revealed that the sponsor did not conduct appropriate monitoring that could capture the above cases of violation of inclusion criteria. PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

IV. Overall Evaluation

Based on the submitted data, the efficacy of febuxostat in the treatment of hyperuricemia has been demonstrated and its safety is acceptable in view of its observed benefits. Febuxostat, as a uric acid production inhibitor, offers a new therapeutic option for patients with hyperuricemia and is considered to have clinical significance. The occurrence of gouty arthritis, adverse events related to thyroid function, liver function, or the cardiovascular system following treatment with febuxostat, and safety in patients with renal or hepatic impairment, elderly patients, and women etc. need to be further investigated via post-marketing surveillance.

This application may be approved if febuxostat is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

November 5, 2010

I. Product Submitted for Registration

Brand Name	Feburic Tablet 10 mg Feburic Tablet 20 mg Feburic Tablet 40 mg
Non-proprietary Name	Febuxostat
Applicant	Teijin Pharma Limited
Date of Application	December 25, 2009

II. Content of the Review

The comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

(1) Cardiovascular risk

PMDA's view:

There are limitations in the evaluation of cardiovascular risk in Japanese patients receiving febuxostat because (i) the Japanese clinical study data on the incidence of cardiovascular adverse events [see Table 33 in the Review Report (1)] suggested no trend towards a particularly higher incidence in the febuxostat group than that in the placebo or allopurinol group, but the data were obtained based on a limited number of subjects, and (ii) short treatment durations (8 or 16 weeks) were used in the 5 Japanese clinical studies. In addition, the *Japanese Treatment Guideline* 2nd ed. states that elevated serum urate levels have been reported to correlate with an independent cardiovascular risk while it also states that changes in serum urate levels have been reported to be a sheer consequence of cardiovascular risk factors. Therefore, the degree of elevation of cardiovascular risk in patients with hyperuricemia and its ethnic differences do not seem to have been elucidated at present. Based on the above, close attention should be paid to foreign post-marketing safety data of febuxostat and data from ongoing foreign post-marketing studies evaluating cardiovascular risk associated with febuxostat, and information on cardiovascular adverse events should continue to be collected by Japanese post-marketing surveillance planned to generate data allowing for comparison with foreign data. The above conclusion by PMDA was supported by the expert advisors.

Based on the above, PMDA requested the applicant to collect information on cardiovascular risk by post-marketing surveillance.

The applicant's response:

Cardiovascular outcome studies were conducted as parallel-group studies to compare febuxostat and allopurinol in patients with cardiovascular risk, and evaluated [redacted] subjects per group for a maximum of [redacted] years in the U.S. and [redacted] subjects per group for an average of [redacted] years in Europe. A specified drug use-results survey regarding long-term use of febuxostat will be conducted with an observation period of 156 weeks (approximately 3 years) and a sample size of 3000 so that cross-reference to the data from the febuxostat group in the cardiovascular outcome studies can be made. This survey will collect data on typical cardiovascular risk factors such as age, sex, BMI, medical history, lifestyle including alcohol consumption and smoking, glucose/lipid metabolism status, and use and type of concomitant drugs. The survey will also investigate cardiovascular-related events as an independent survey item separately from adverse events in general. The cardiovascular-related events will be defined using major adverse cardiovascular events (MACE) composite that was the primary endpoint in the outcome study in the U.S. Participants in this survey have characteristics different from those who

participated in the foreign cardiovascular outcome studies, which were conducted in patients with cardiovascular risk. Taking into account dropouts during observation and assuming an average observation period of [redacted] years, the number of deaths from cerebrovascular and cardiovascular causes expected in this survey is approximately 20 to 30 because (i) 0.0039 deaths from cerebrovascular and cardiovascular causes per patient-year expected to occur in the Japanese general population aged ≥30 years (Sakata K, et al, *Eur J Epidemiol.* 2001;17:461-468) leads to the expected number of deaths from cerebrovascular and cardiovascular causes of 17.6 (= 3000 patients × [redacted] years × 0.0039/patient-year), and (ii) the coronary mortality and cerebrovascular mortality among patients with serum urate levels >8.5 mg/mL have been found to be 1.52- and 2.33-fold, respectively, higher than those among patients with serum urate levels of 5.0 to <6.4 mg/mL (Tomita M, et al, *J Epidemiol.* 2000;10:403-409). Furthermore, it is likely that the use of MACE, which includes cerebrovascular and cardiovascular events other than death, as the endpoint will lead to a rise in the number of deaths to more than the expected number of 20 to 30. Therefore, information will be collected on cardiovascular events in the Japanese population including not only MACE cases to be detected by this survey but also spontaneously reported MACE cases to assess cardiovascular risk associated with febuxostat in the Japanese population.

PMDA accepted the applicant's response.

(2) Indication

PMDA's view:

Febuxostat belongs to the same class as that of allopurinol, which is an approved drug with extensive clinical use in and out of Japan. At present, no worldwide consensus has been reached on the need for or significance of treatment of hyperuricemia without gouty arthritis or tophi. However, in clinical settings in Europe (excluding the U.K.) and Japan, allopurinol has been prescribed for patients with hyperuricemia more frequently than for gout patients, evidencing a certain level of recognition of the need for or significance of treatment of hyperuricemia. Febuxostat is indicated only for gout in the U.S., Europe, and South Korea based on the results of clinical studies conducted exclusively in gout patients in the U.S., while Japanese clinical studies of febuxostat were conducted in patients with hyperuricemia including gout and demonstrated the efficacy of febuxostat. In addition, given the therapeutic indications of urate-lowering agents recommended in the *Japanese Treatment Guideline* 2nd ed., there is no significant problem with including, in addition to gout patients, patients with serum urate levels ≥8.0 mg/dL who have complications such as hypertension, ischemic heart disease, or diabetes mellitus, which are potential risk factors for renal (including urinary calculus) or cardiovascular disorders, and patients with serum urate levels ≥9.0 mg/dL even after lifestyle modifications in the intended population for febuxostat. Taking into account the above points and the fact that the definition of hyperuricemia specified in the *Japanese Treatment Guideline* 2nd ed. (serum urate level >7.0 mg/dL) includes gout patients requiring medical treatment, the proposed indication ("Improvement of hyperuricemia in the following diseases: gout, hyperuricemia") should be modified to "Hyperuricemia," and the Precautions for Indications section of the package insert should state that "Feburic should be used for gout patients requiring medical treatment or patients who have renal impairment (including urinary calculus) or complications such as hypertension, ischemic heart disease, and diabetes mellitus according to the *Therapeutic Policy for the Management of Hyperuricemia* by the Japanese Society of Gout and Nucleic Acid Metabolism." In addition, the Precautions for Indications section of the package insert should state that the safety and efficacy have not been established in female patients, because clinical experience of febuxostat in female patients is limited as the numbers of male and female subjects were 453 and 8, respectively, in the 5 Japanese clinical studies, and 460 and 14, respectively, in the 2 Japanese long-term treatment studies. The above conclusion by PMDA was largely supported by the expert advisors. Some expert advisors provided the following comments:

- It's preferable at present to avoid including descriptions that restrict the intended population because guidelines may be modified as science progresses.
- The intended population should include gout patients with serum urate levels ≤7.0 mg/dL with recurrent gouty arthritis, who will be excluded if the labeled indication is stated as "Hyperuricemia." Therefore, the Indication section should state "Gout and/or hyperuricemia."
- Confusion may occur in clinical setting if the indication for febuxostat is stated as "Hyperuricemia" only, because the indications for approved urate-lowering agents have included gout.

PMDA's view:
Although allopurinol acts by the same mechanism of action as that of febuxostat, it is an old drug approved in December 1968, when definitions of gout and hyperuricemia, their indications for medical treatment, and conduct of clinical studies were probably different from those used currently. Therefore, there is less need to align the indication for febuxostat with that for allopurinol in light of currently available scientific findings, and confusion in clinical setting can be avoided by providing an appropriate precautionary statement even when indications for the two drugs are not aligned with each other. Meanwhile, the *Japanese Treatment Guideline* 2nd ed. states that patients with recurrent gouty arthritis or with tophi are eligible for medical treatment and that it is preferable patients have their serum urate levels maintained at ≤6.0 mg/dL, but some of such patients may fall outside the definition of hyperuricemia as specified in the *Japanese Treatment Guideline* 2nd ed. (serum urate level >7.0 mg/dL) and may require medical treatment due to difficulty in removing urate accumulated in the body through lifestyle guidance alone; and thus, there are some clinical significances in including gout in the indication of febuxostat. There are no significant problems with not specifically using a description "Amelioration of blood urate levels in patients with gout and/or hyperuricemia" for the Indication section for the following reasons: a precautionary statement that "Even if gouty arthritis (gout attack) occurred on treatment with Feburic, Feburic should be continued without dose modification, and colchicine, non-steroidal anti-inflammatory drugs, and/or corticosteroids should be used depending on the patient's symptoms" is included in the Important Precautions section; and approved urate-lowering agents such as allopurinol are considered to be recognized by healthcare professionals as drugs for amelioration of blood urate levels rather than for treatment of gouty arthritis because all of those agents have been on the market for ≥20 years. Based on the above, PMDA requested the applicant to incorporate the following modifications to the descriptions in the Indication and the Precautions for Indications sections of the package insert. The applicant accepted the request, and thus, PMDA accepted the applicant's response.

(Modified descriptions)
Indication
Gout and hyperuricemia

Precautions for Indications

(1) Feburic should be used for patients requiring medical treatment according to current treatment guidelines.

(2) The safety and efficacy have not been established in female patients. [Clinical experience is limited.]

(3) Dosage and Administration
PMDA's view:
The efficacy and safety were evaluated in studies conducted using the dose escalation scheme selected at the early developmental phase and studies conducted using the new dose escalation scheme selected after withdrawal of regulatory application. In light of the evaluation, there is no problem with the applicant's view that febuxostat should be orally administered once daily at unspecified timing relative to meals with the initial, usual, and maximum dose levels being 10, 40, and 60 mg/day, respectively. However, for the purpose of reducing the incidence of gouty arthritis caused by an abrupt reduction of serum urate levels, the Dosage and Administration section should include statement that the dose should be started at 10 mg/day and then be gradually increased and the "Precautions for Dosage and Administration" section should include description of the specific scheme (dose levels and durations) for dose escalation up to the usual dose (40 mg/day). The above conclusion by PMDA was largely supported by the expert advisors. Some expert advisors commented that based on the clinical study data, dose increase to 40 mg/day may not be necessary in some patients and it is preferable to provide an additional statement that the dose should be increased while monitoring the patient's serum urate level. Based on the above, PMDA requested the applicant to incorporate the following modifications to the descriptions in the Dosage and Administration and the Precautions for Dosage and Administration sections of the package insert. The applicant accepted the request, and PMDA accepted the applicant's response.

(Modified descriptions)

Dosage and Administration

The usual initial adult dosage is 10 mg of febuxostat administered orally once daily. The dose should be gradually increased as necessary, while monitoring blood urate levels. The usual maintenance dose should be 40 mg once daily. The dose may be adjusted according to the patient's condition. The maximum dose should be 60 mg once daily.

Precautions for Dosage and Administration

A rapid fall in blood urate levels may induce gouty arthritis (gout attack) during the early phase of treatment with a urate-lowering agent. Feburic should be started at 10 mg once daily and the dose should be gradually increased to, for example, 20 mg once daily after the first 2 weeks and 40 mg once daily after 6 weeks of treatment (see "Clinical Studies"). Patients with a dose increase should be carefully monitored.

(4) Co-administration of febuxostat with azathioprine or 6-mercaptopurine

PMDA concluded that co-administration of febuxostat with azathioprine or 6-mercaptopurine should be contraindicated because no clinical drug interaction studies of febuxostat with the drugs have been conducted and that there can be no assurance of the safety of concomitant use of febuxostat with azathioprine or 6-mercaptopurine administered at an approximately 3- to 6-fold lower dose level than usual. The above conclusion by PMDA was supported by the expert advisors. Based on the above, PMDA requested the applicant to contraindicate febuxostat in patients on treatment with azathioprine or 6-mercaptopurine. The applicant accepted the request, and PMDA accepted the applicant's response.

(5) Post-marketing surveillance plans

PMDA's view:

The limited experience with febuxostat in clinical studies mandates continued collection of information on the occurrence of gouty arthritis, adverse events related to thyroid function, liver function, or the cardiovascular system following treatment with febuxostat, and safety and efficacy in patients with renal or hepatic impairment, elderly patients, and women by post-marketing surveillance. For assessment of cardiovascular risk in particular, an observation period of ≥3 years is appropriate to allow for comparison with foreign data. The above conclusion by PMDA was supported by the expert advisors. Based on the above, PMDA requested the applicant to resubmit a draft post-marketing surveillance plan.

The applicant's response:

A specified drug use-results survey with an observation period of 3 years and a target sample size of 3000 will be conducted to collect information on the efficacy, safety, and proper use of long-term treatment with febuxostat in routine clinical settings. The Incidence and outcome of gouty arthritis will be recorded separately from those of other adverse events in general under an independent survey item "Assessment of gouty arthritis," collecting information on change in urate levels over time and on drugs used at the onset of and for treatment of gouty arthritis. Thyroid or liver function-related adverse events during the observation period will be considered to be adverse events in general and recorded along with their course, intervention administered, outcome, and associated laboratory data (thyroid function parameters including TSH, FT_3, and FT_4, and liver function parameters including AST, ALT, and γ-GTP). This survey will also investigate cardiovascular risk [see "(1) Cardiovascular risk"]. For patients with renal impairment, information on the use of dialysis and laboratory values including BUN, serum creatinine, β_2-microglobulin, and NAG will be collected, and the incidence of adverse events and serum urate levels stratified by eGFR will be analyzed. For patients with hepatic impairment, information on laboratory values including AST, ALT, and γ-GTP will be collected, and the safety and efficacy stratified by the hepatic impairment will be analyzed. Collection and analyses of safety and efficacy information will be performed also for elderly and female patients within the framework of this survey. Based on the percentage of female patients (2.3% [24 of 1027 patients]) who participated in Japanese clinical studies, approximately 70 female patients are expected to be collected through this survey.

PMDA accepted the applicant's response.

(6) Shelf life for the drug product

The applicant submitted the [redacted]-month data from an ongoing long-term testing (25°C/60% RH) of 40 mg tablets (PTP package or polyethylene bottle [500 tablets]) ([redacted]), and explained the stability of the drug product as follows:

The proposed shelf life of 36 months for the drug product is appropriate in light of the stability results showing no apparent changes from initial value for any batches regardless of packaging configuration and of the extrapolated shelf life obtained based on the long-term stability data up to [redacted] months according to "Guideline on Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004, dated June 3, 2003).

PMDA concluded that the proposed shelf life of 36 months for the drug product is acceptable.

(7) Brand name

The proposed Japanese brand name was changed from *Feburikku* to *Feburiku* at the request of the applicant. This does not affect the English brand name.

III. Overall Evaluation

As a result of the above review, PMDA concluded that this product may be approved after modifying the indication, and dosage and administration statements as shown below. The re-examination period is 8 years. Neither the drug substance nor the drug product is classified as a poisonous drug or a powerful drug, and the drug product is not classified as a biological product or a specified biological product.

Indication	Gout and hyperuricemia
Dosage and Administration	The usual initial adult dosage is 10 mg of febuxostat administered orally once daily. The dose should be gradually increased as necessary, while monitoring blood urate levels. The usual maintenance dose should be 40 mg once daily. The dose may be adjusted according to the patient's condition. The maximum dose should be 60 mg once daily.