**Report on the Deliberation Results**

May 16, 2016

Evaluation and Licensing Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

| | |
|---|---|
| **Brand Name** | Feburic Tablets 10 mg<br>Feburic Tablets 20 mg<br>Feburic Tablets 40 mg |
| **Non-proprietary Name** | Febuxostat (JAN*) |
| **Applicant** | Teijin Pharma Limited |
| **Date of Application** | July 29, 2015 |

**Results of Deliberation**
In the meeting held on April 20, 2016, the First Committee on New Drugs concluded that the partial change application for the product may be approved and that the re-examination period is 4 years.

**Conditions of Approval**
The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

**Review Report**

April 4, 2016

Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency.

| | |
|---|---|
| **Brand Name** | Feburic Tablets 10 mg<br>Feburic Tablets 20 mg<br>Feburic Tablets 40 mg |
| **Non-proprietary Name** | Febuxostat |
| **Applicant** | Teijin Pharma Limited |
| **Date of Application** | July 29, 2015 |
| **Dosage form/Strength** | Tablets: Each tablet contains 10, 20, or 40 mg of Febuxostat. |
| **Application Classification** | Prescription drug (4) Drug with a new indication (6) Drug with a new dosage |
| **Items Warranting Special Mention** | None |
| **Reviewing Office** | Office of New Drug I |

**Results of Review**

As shown in the Attachment, 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 hyperuricemia associated with cancer chemotherapy has been demonstrated and its safety is acceptable in view of its observed benefits.

As a result of its regulatory review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions.

**Indications**

1. Gout and hyperuricemia
2. Hyperuricemia associated with cancer chemotherapy

(Underline denotes additions.)

**Dosage and Administration**

1. Gout and hyperuricemia

The usual initial adult dosage is 10 mg of febuxostat administered orally once daily. Then, the dose should be gradually increased, as necessary, with blood urate levels monitored. 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.

2. Hyperuricemia associated with cancer chemotherapy

The usual adult dosage is 60 mg of febuxostat administered orally once daily.

(Underline denotes additions.)

**Conditions of Approval**

The applicant is required to develop and appropriately implement a risk management plan.

**Attachment**

**Review Report (1)**

February 25, 2016

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency.

**Product Submitted for Registration**

| | |
|---|---|
| **Brand Name** | Feburic Tablets 10 mg<br>Feburic Tablets 20 mg<br>Feburic Tablets 40 mg |
| **Non-proprietary Name** | Febuxostat |
| **Applicant** | Teijin Pharma Limited |
| **Date of Application** | July 29, 2015 |
| **Dosage form/Strength** | Tablets: Each tablet contains 10, 20, or 40 mg of Febuxostat. |
| **Proposed Indication** | 1. Gout and hyperuricemia<br>2. Prevention of hyperuricemia associated with cancer chemotherapy<br>(Underline denotes additions.) |

**Proposed Dosage and Administration**

1. Gout and hyperuricemia

The usual initial adult dosage is 10 mg of febuxostat orally administered once daily. Then, the dose should be gradually increased, as necessary, with blood urate levels monitored. 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.

2. Prevention of hyperuricemia associated with cancer chemotherapy

The usual adult dosage is 60 mg of febuxostat administered orally once daily.

(Underline denotes additions.)

**Table of Contents**

**List of Abbreviations**

| | |
|---|---|
| Adverse drug reaction | Adverse events for which a causal relationship to the study drug could not be ruled out |
| ALT | Alanine Aminotransferase |
| AST | Aspartate Aminotransferase |
| AUC | Area under the Concentration Time Curve |
| CTCAE v4.0-JCOG | Common Terminology Criteria for Adverse Events v4.0-Japan Clinical Oncology Group |
| CTLS | Clinical Tumor Lysis Syndrome |
| eGFR | Estimated Glomerular Filtration Rate |
| FAS | Full Analysis Set |
| Feburic | Feburic Tablets |
| Febuxostat | Febuxostat |
| GCP | Good Clinical Practice |
| Japanese clinical guidance for treatment of TLS | The Japanese Society of Medical Oncology eds. *Clinical Guidance for Treatment of Tumor Lysis Syndrome (TLS)* [in Japanese]. Kanehara & Co., Ltd.; 2013 |
| LOCF | Last Observation Carried Forward |
| LDH | Lactate Dehydrogenase |
| LTLS | Laboratory Tumor Lysis Syndrome |
| MedDRA | Medical Dictionary for Regulatory Activities |
| Rasburicase | Rasburicase (Genetical Recombination) |
| SOC | System Organ Class |
| TLS | Tumor Lysis Syndrome |
| TLS panel consensus | TLS panel consensus (*Br J Haematol*. 2010;149:578-86) |
| PMDA | Pharmaceuticals and Medical Devices Agency |
| Serum urate AUC | Area under the serum urate concentration-time curve |

## 1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Febuxostat, a xanthine oxidase inhibitor discovered by Teijin Pharma Limited (formerly Teijin Limited), is the active ingredient of an oral drug product Feburic Tablets (hereinafter referred to as Feburic). Feburic was approved in January 2011 for the indication of "gout and hyperuricemia."

A rapid lysis of tumor cells during cancer chemotherapy leads to a massive release of intracellular materials including nucleic acids, potassium, phosphorus, and proteins into circulating blood, which may in turn cause tumor lysis syndrome (TLS), characterized by hyperuricemia, electrolyte abnormalities such as hyperkalemia and hyperphosphatemia, renal disorders, and the resultant multi-organ failure. In particular, in patients with hyperuricemia associated with chemotherapy, decrease in urinary pH enhances formation of urate crystals in the renal tubules, and the deposited urate crystals may cause tubular obstruction leading to acute renal failure or death. In addition, patients with high serum urate levels have been reported to be at high risk of TLS and renal impairment (*J Clin Oncol.* 2008;26:2767-2778). Development of TLS would compromise subsequent cancer therapy, and therefore, adequate control of serum urate levels is considered clinically important in chemotherapy.

In Japan, Rasburicase (Genetical Recombination) [rasburicase], a urate-degrading enzyme preparation, was approved for the treatment of hyperuricemia associated with chemotherapy in October 2009. Meanwhile, the Japanese Society of Medical Oncology eds. *Clinical Guidance for Treatment of Tumor Lysis Syndrome [TLS]* [in Japanese], Kanehara & Co., Ltd., 2013 (Japanese clinical guidance for treatment of TLS) recommends treatment with drugs including allopurinol, a uric acid production inhibitor, but these drugs are not approved for the indication of hyperuricemia associated with chemotherapy.

The applicant has now submitted an application for a partial change approval because the efficacy and safety of Feburic in patients with hyperuricemia associated with chemotherapy have been demonstrated through a Japanese phase III study.

Feburic was approved in Europe in April 2015 for the indication of hyperuricemia associated with chemotherapy in patients with hematologic malignancies at an intermediate to high risk of TLS, and is approved in 33 countries as of January 2016.

## 2. Data Relating to Quality and Outline of the Review Conducted by PMDA

Since this application relates to new indications and dosage, data relating to quality were not submitted.

## 3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

Although this application relates to new indications and dosage, no new study data were submitted because review of non-clinical pharmacology data was completed at the time of initial approval.

## 4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

Although this application relates to new indications and dosage, no new study data were submitted because review of non-clinical pharmacokinetic data was completed at the time of initial approval.

## 5. Toxicity and Outline of the Review Conducted by PMDA

Since this application relates to new indications and dosage, toxicity data were not submitted.

## 6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

Although this application relates to new indications and dosage, no new study data were submitted because reviews of data on biopharmaceutic studies and associated analytical methods and clinical pharmacology study data were completed at the time of initial approval.

## 7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted evaluation data, namely the results from a Japanese phase III study (Study TMX-67TLS-01) and reference data, namely the results from a foreign phase III study (Study FLO-01). Primary study results are shown below.

### 7.1 Japanese phase III study (CTD 5.3.5.1-1, Study TMX-67TLS-01 [January to September 2014])

A randomized, open-label, allopurinol-controlled parallel-group comparative study was conducted to evaluate the efficacy and safety of febuxostat in patients with malignant tumors who were planning to receive chemotherapy (target sample size, 100 subjects [50/group]).

Key inclusion criteria were patients aged ≥20 years who were planning to receive chemotherapy for malignant tumors (including molecular targeted therapies) at an intermediate or high risk (patients who are not planning to receive rasburicase) of TLS.[1)]

Subjects received febuxostat 60 mg once daily (qd) orally after breakfast or allopurinol 100 mg thrice daily (tid), i.e. 300 mg/day, orally after each meal. Subjects in the allopurinol group whose estimated glomerular filtration rate (eGFR) was ≥30 to <45 mL/min/1.73 $m^2$ at registration received allopurinol 100 mg of twice daily (bid), i.e. 200 mg/day, orally after morning and evening meals. Subjects received treatment from 24 hours prior to initiation of chemotherapy for malignant tumors for 6 days, and the treatment duration was allowed to be extended up to 14 days at the discretion of the investigator.

Of all 100 treated subjects, 99 subjects (49 in the febuxostat group, 50 in the allopurinol group) were included in the safety analysis set and the Full Analysis Set (FAS). One subject was excluded (in the allopurinol group) because of a Good Clinical Practice (GCP) violation (inadequate written informed consent process). The FAS was also for the primary efficacy analysis. Two subjects (in the allopurinol group) discontinued the study; the reasons included an adverse event in 1 subject and a failure to receive a specified dose of the study drug prior to the initiation of chemotherapy in 1 subject.[2)]

The area under the serum urate concentration-time curve (serum urate AUC) from baseline (start of study treatment) to Day 6 in FAS, the primary efficacy endpoint, is shown in Table 1. The least squares mean [two-sided 95% confidence interval (CI)] of the between-group difference (febuxostat group - allopurinol group) in the serum urate AUC from baseline to Day 6 was -33.61 [-70.67, 3.45] mg·h/dL, showing non-inferiority of febuxostat over allopurinol.[3)] The time course of serum urate level is shown in Figure 1.

**Table 1. Serum urate AUC from baseline to Day 6 (FAS)**

| Treatment group | Serum urate level (mg/dL) | | Serum urate AUC (mg·h/dL)[a) b)] | Between-group difference[b)] |
|---|---|---|---|---|
| | Baseline | Day 6[a)] | | |
| Febuxostat (N = 49) | 5.65 ± 1.35 | 2.55 ± 1.20 | 479.82 ± 13.26 | -33.61 [-70.67, 3.45] |
| Allopurinol (N = 50) | 5.52 ± 1.76 | 2.67 ± 1.04 | 513.44 ± 13.13 | - |

Serum urate levels, Mean ± standard deviation (SD)
Serum urate AUC, Least squares mean ± standard error or least squares mean [two-sided 95% CI]
a) Missing data were imputed using LOCF.
b) Analysis of covariance model with treatment group as a factor and baseline serum urate level as a covariate

1) Determined based on the primary disease (e.g., solid tumors, multiple myeloma, leukemia, and malignant lymphoma), stage/type, white blood cell count, lactate dehydrogenase (LDH) level, renal function, and urate level, etc., referring to the TLS panel consensus.
2) Subjects were to receive febuxostat or allopurinol at the predetermined dose (120 mg for febuxostat and 400 mg [300 mg in subjects with renal impairment] for allopurinol) on the previous day and the day of initiation of chemotherapy; subjects were to be withdrawn from the study if they miss these doses.
3) Treatment difference was defined as "allopurinol group minus febuxostat group" in the study protocol, but the results were presented as "febuxostat group minus allopurinol group." The non-inferiority margin was determined based on the serum urate AUC from baseline to Day 6 and the baseline urate level (6.5 mg/dL) in 9 subjects receiving febuxostat in a Japanese clinical study (*Anticancer Research*. 2014;34:7287-96). Based on the data of this study, serum urate AUC was expected to be 610 mg·h/dL in the allopurinol group, and on the assumption of serum urate remaining at a certain level, serum urate AUC was expected to be 936 mg·h/dL in the placebo group. The non-inferiority margin was defined as a value less than or equal to one half the difference (326 mg·h/dL) in serum urate AUC between the allopurinol and placebo groups.

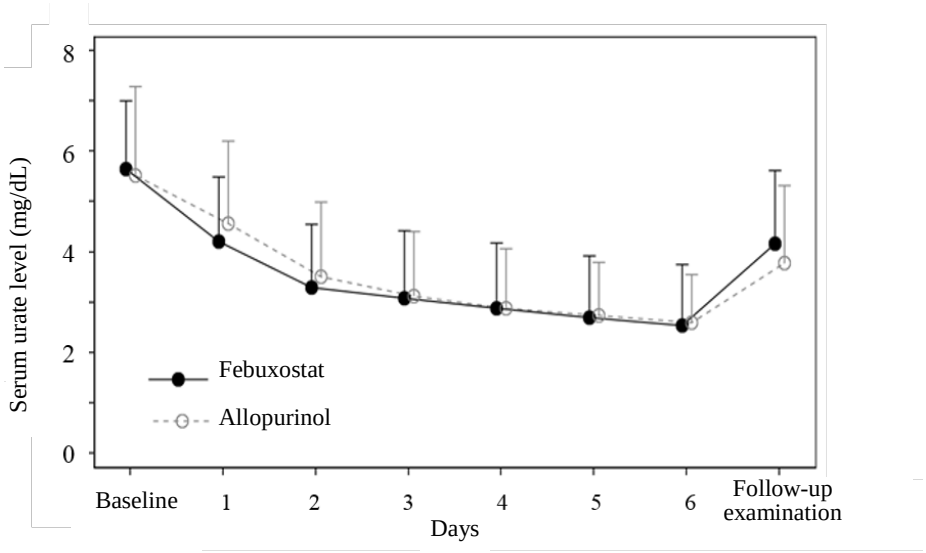


**Figure 1. Time course of serum urate level (FAS) (mean ± SD)**
**(*The follow-up examination was performed at 7 days after the last dose of the study drug)**

The results of secondary endpoints are shown in Table 2.

**Table 2. Results of secondary endpoints (FAS)**

| Endpoint | Febuxostat (N = 49) | | Allopurinol (N = 50) | |
|---|---|---|---|---|
| | At the start of treatment | After 6 days of treatment[a)] | At the start of treatment | After 6 days of treatment[a)] |
| Serum urate level (mg/dL) | 5.65 ± 1.35 | 2.55 ± 1.20 | 5.52 ± 1.76 | 2.67 ± 1.04 |
| Serum LDH (U/L) | 414.9 ± 273.2 | 303.8 ± 176.0 | 371.5 ± 222.9 | 277.1 ± 170.9 |
| Serum creatinine (mg/dL) | 0.799 ± 0.233 | 0.764 ± 0.218 | 0.766 ± 0.198 | 0.708 ± 0.170 |
| Serum potassium (mEq/L) | 4.13 ± 0.42 | 4.12 ± 0.51 | 4.27 ± 0.41 | 4.12 ± 0.48 |
| Serum calcium (mg/dL) | 8.69 ± 0.69 | 8.47 ± 0.60 | 8.81 ± 0.71 | 8.39 ± 0.63 |
| Serum phosphorus (mg/dL) | 3.42 ± 0.49 | 3.45 ± 0.72 | 3.50 ± 0.61 | 3.37 ± 0.81 |

Mean ± SD
a) Missing data were imputed using LOCF.

Evaluation of the incidence of TLS,[4)] another secondary endpoint, revealed that the percentage of subjects who experienced TLS during the period from baseline to Day 6 was 2.0% (1 of 49 subjects) in the febuxostat group and 4.0% (2 of 50 subjects) in the allopurinol group.

The incidence of adverse events and adverse events for which a causal relationship to the study drug could not be ruled out (adverse drug reactions) were 93.9% (46 of 49) of subjects and 2.0% (1 of 49) of subjects, respectively, in the febuxostat group, and 96.0% (48 of 50) of subjects and 2.0% (1 of 50) of subjects, respectively, in the allopurinol group. The incidence of adverse events reported by ≥5% of subjects in either group is shown in Table 3. Two adverse drug reactions (alanine aminotransferase [ALT] increased/aspartate aminotransferase [AST] increased) were reported by 1 subject in the febuxostat group and 1 adverse drug reaction (ALT increased) was reported by 1 subject in the allopurinol group.

4) TLS is broadly classified into Laboratory TLS (LTLS) and Clinical TLS (CTLS). LTLS was defined as TLS in patients who met ≥2 of the following conditions: Hyperuricemia, hyperkalemia, or hyperphosphatemia (determined by test values that exceed the upper limit of normal). CTLS was defined as TLS in LTLS patients who met any one of the following conditions: Serum creatinine of ≥1.5 times the upper limit of normal, arrhythmia, convulsion, or death.

**Table 3. Incidence of adverse events reported by ≥5% of subjects in either group (safety analysis set)**

| Event term | Febuxostat (N = 49) | Allopurinol (N = 50) |
|---|---|---|
| Overall adverse events | 93.9 (46) | 96.0 (48) |
| White blood cell count decreased | 53.1 (26) | 54.0 (27) |
| Constipation | 32.7 (16) | 58.0 (29) |
| Nausea | 28.6 (14) | 26.0 (13) |
| Neutrophil count decreased | 26.5 (13) | 24.0 (12) |
| Malaise | 20.4 (10) | 28.0 (14) |
| Decreased appetite | 18.4 (9) | 28.0 (14) |
| Lymphocyte count decreased | 18.4 (9) | 22.0 (11) |
| Hyperglycaemia | 16.3 (8) | 16.0 (8) |
| Diarrhoea | 14.3 (7) | 14.0 (7) |
| Platelet count decreased | 12.2 (6) | 28.0 (14) |
| Febrile neutropenia | 12.2 (6) | 12.0 (6) |
| Anaemia | 10.2 (5) | 22.0 (11) |
| Weight increased | 10.2 (5) | 6.0 (3) |
| Hepatic function abnormal | 8.2 (4) | 16.0 (8) |
| Hiccups | 8.2 (4) | 14.0 (7) |
| Insomnia | 8.2 (4) | 10.0 (5) |
| Leukopenia | 8.2 (4) | 6.0 (3) |
| Oedema | 8.2 (4) | 2.0 (1) |
| Vomiting | 8.2 (4) | 2.0 (1) |
| Abdominal discomfort | 6.1 (3) | 6.0 (3) |
| Pyrexia | 6.1 (3) | 4.0 (2) |
| Blood urea increased | 6.1 (3) | 4.0 (2) |
| Bone marrow failure | 6.1 (3) | 4.0 (2) |
| Infusion related reaction | 6.1 (3) | 2.0 (1) |
| Stomatitis | 4.1 (2) | 12.0 (6) |
| Oedema peripheral | 4.1 (2) | 10.0 (5) |
| Hyponatraemia | 4.1 (2) | 6.0 (3) |
| Dysgeusia | 4.1 (2) | 6.0 (3) |
| Neutropenia | 2.0 (1) | 8.0 (4) |
| Neuropathy peripheral | 2.0 (1) | 6.0 (3) |
| Hypokalaemia | 0.0 (0) | 8.0 (4) |
| Peripheral sensory neuropathy | 0.0 (0) | 8.0 (4) |
| Alopecia | 0.0 (0) | 6.0 (3) |

Incidence % (n); MedDRA ver.16.0

No deaths were reported. Two serious adverse events (sepsis and cryptococcal fungaemia) were reported by 2 subjects in the allopurinol group, for which a causal relationship to the study drug was ruled out. One adverse event leading to treatment discontinuation (diarrhoea) was reported by 1 subject in the allopurinol group, for which a causal relationship to the study drug was ruled out.

## 7.R Outline of the review conducted by PMDA

### 7.R.1 Efficacy

The applicant's explanation:

In Japanese Study TMX-67TLS-01, the non-inferiority of febuxostat over allopurinol was demonstrated in terms of the serum urate AUC from baseline to Day 6 (primary endpoint). Allopurinol, not approved for the indication of hyperuricemia associated with chemotherapy in Japan, was used as the comparator drug because (i) the TLS panel consensus (*Br J Haematol.* 2010;149:578-586) that was advocated by an international expert committee in 2010 recommended allopurinol, a uric acid production inhibitor, mainly for treatment of patients at an intermediate risk of TLS, and (ii) allopurinol has been widely used in clinical practice in Japan.

Table 4 shows efficacy analysis of the serum urate AUC from baseline to Day 6 by patient characteristic subgroup. No substantial between-group difference in the efficacy was seen in any of the subgroups in terms of baseline serum urate level, primary disease, baseline eGFR, sex, and age. Rasburicase has been recommended for patients at a high risk of TLS, while uric acid production inhibitors have been recommended for patients at a high risk of TLS who are unable to take rasburicase. The Japanese Study TMX-67TLS-01 was conducted in patients at an intermediate and high (patients who are not planning to receive rasburicase) risk of TLS. The efficacy data from the study revealed that there was no between-group difference in the serum urate AUC among intermediate risk patients and that serum urate AUC

was lower in the febuxostat group than in the allopurinol group among high risk patients. Since the between-group difference in serum urate AUC was attributed to the difference in baseline serum urate levels, the serum urate AUC appears to be similar between the treatment groups.

**Table 4. Serum urate AUC from baseline to Day 6 by patient characteristics (Study TMX-67TLS-01, FAS)**

| Patient characteristics | | Febuxostat (N = 49) | | | Allopurinol (N = 50) | | |
|---|---|---|---|---|---|---|---|
| | | n | Baseline serum urate level (mg/dL) | Serum urate AUC (mg·h/dL) | n | Baseline serum urate level (mg/dL) | Serum urate AUC (mg·h/dL) |
| Serum urate level at baseline (mg/dL) | ≤7.0 | 43 | 5.29 ± 0.97 | 448.72 ± 148.30 | 41 | 4.94 ± 1.24 | 458.90 ± 152.95 |
| | >7.0 | 6 | 8.27 ± 0.54 | 754.80 ± 60.61 | 9 | 8.19 ± 1.23 | 727.20 ± 161.16 |
| Category of risk of TLS | Intermediate | 34 | 5.62 ± 1.19 | 475.66 ± 142.63 | 35 | 5.00 ± 1.38 | 464.40 ± 170.66 |
| | High | 15 | 5.71 ± 1.70 | 510.08 ± 231.71 | 15 | 6.74 ± 1.98 | 607.04 ± 183.41 |
| Primary disease | Leukemia | 5 | 6.20 ± 1.29 | 633.84 ± 160.28 | 5 | 6.94 ± 3.06 | 637.20 ± 248.68 |
| | Lymphoma | 33 | 5.48 ± 1.34 | 456.58 ± 165.25 | 33 | 5.37 ± 1.50 | 484.47 ± 180.38 |
| | Solid tumors | 11 | 5.90 ± 1.42 | 507.93 ± 177.67 | 12 | 5.36 ± 1.68 | 515.50 ± 160.65 |
| Baseline eGFR (mL/min/1.73 $m^2$) | <45 | 1 | 5.80 | 552.00 | 3 | 8.07 ± 1.48 | 840.40 ± 187.36 |
| | ≥45 to <60 | 10 | 6.14 ± 1.69 | 525.96 ± 175.41 | 13 | 5.80 ± 1.59 | 529.48 ± 162.28 |
| | ≥60 to <90 | 30 | 5.79 ± 1.20 | 490.96 ± 169.10 | 25 | 5.16 ± 1.41 | 470.59 ± 167.97 |
| | ≥90 | 8 | 4.49 ± 0.92 | 410.40 ± 193.58 | 9 | 5.28 ± 2.37 | 465.60 ± 166.91 |
| Sex | Male | 30 | 6.20 ± 1.29 | 558.56 ± 143.82 | 27 | 5.69 ± 1.76 | 561.51 ± 200.69 |
| | Female | 19 | 4.78 ± 0.93 | 371.94 ± 154.62 | 23 | 5.33 ± 1.77 | 443.43 ± 143.72 |
| Age | <65 years | 20 | 5.92 ± 1.40 | 545.70 ± 179.68 | 14 | 5.61 ± 1.84 | 495.77 ± 155.29 |
| | ≥65 years | 29 | 5.47 ± 1.30 | 445.16 ± 158.37 | 36 | 5.49 ± 1.75 | 511.63 ± 197.04 |

Mean ± SD

Since the clinical aim of controlling serum urate levels is to reduce development of acute renal failure associated with TLS, PMDA asked the applicant to explain the incidence of TLS and renal impairment-related events.

The applicant's response:
The Japanese clinical guidance for treatment of TLS recommends that TLS panel consensus be used as diagnostic criteria to classify TLS into categories of Laboratory TLS (LTLS) and Clinical TLS (CTLS). LTLS is defined by the presence of ≥2 conditions of the following during the period from 3 days before to 7 days after the start of chemotherapy: Hyperuricemia, hyperkalemia, or hyperphosphatemia. CTLS is defined by the presence of LTLS in addition to any one of the following clinical symptoms: Renal insufficiency (serum creatinine ≥1.5 times the upper limit of normal [ULN]), arrhythmia, sudden death, or convulsion. Once developed, CTLS requires strict management and intensive treatment. In Japanese Study TMX-67TLS-01, 1 episode of TLS was reported by 1 subject in the febuxostat group and 2 episodes by 2 subjects in the allopurinol group. All episodes were LTLS, and CTLS were not reported. The 1 subject in the febuxostat group and 1 subject in the allopurinol group (300 mg/day) were assessed as having LTLS because the serum potassium and phosphorus levels both exceeded the ULN on Day 3. The other subject in the allopurinol group (200 mg/day), who had serum urate level (9.7 mg/dL) exceeding the ULN at baseline, was assessed as having LTLS because the serum urate and phosphorus levels both exceeded the ULN until Day 3, despite a decrease in the serum urate levels over time seen after the start of treatment. The serum urate and phosphorus levels resolved on Day 4 in this subject. No substantial changes were observed in serum electrolytes in either group during the treatment period (Table 2), and no substantial between-group difference was found in the incidence of metabolic abnormality associated with TLS (Table 5).

**Table 5. Incidence of metabolic abnormality associated with TLS (Study TMX-67TLS-01, safety analysis set)**

| Event term | Febuxostat (N = 49) | Allopurinol (N = 50) |
|---|---|---|
| Hyperkalaemia | 2.0 (1) | 2.0 (1) |
| Hypocalcaemia | 0.0 (0) | 4.0 (2) |
| Blood potassium increased | 2.0 (1) | 0.0 (0) |

Incidence % (n); MedDRA ver.16.0

During the first 6 days of chemotherapy in the foreign phase III study (Study FLO-01[5)]), no substantial between-group difference was found in the incidence of LTLS (8.1% [14 of 173 subjects] in the febuxostat group, 9.2% [16 of 173 subjects] in the allopurinol group) or CTLS (1.7% [3 of 173 subjects] and 1.2% [2 of 173 subjects] in the respective groups).

In terms of renal impairment-related events in Japanese Study TMX-67TLS-01, no patients in either group started dialysis during the study period. Acute kidney injury[6)] was reported by only 1 subject in the febuxostat group, in whom the serum creatinine levels were elevated by ≥0.3 mg/dL from baseline after 3 days of treatment and remained at high levels until after 6 days of treatment. The outcome at the end of the study was "unchanged." The renal impairment in this subject was unlikely to be caused by hyperuricemia associated with tumor lysis because the serum urate levels were below the ULN during the study period. Serum creatinine levels did not change in the febuxostat or allopurinol group and renal function was almost maintained during the treatment period (Table 2).

PMDA's view:
In Japanese Study TMX-67TLS-01, the non-inferiority of febuxostat over allopurinol was demonstrated in terms of the serum urate AUC from baseline to Day 6, the primary endpoint. Therefore, PMDA concluded that the efficacy of febuxostat in patients with hyperuricemia associated with chemotherapy has been demonstrated. Although the comparator drug allopurinol has not been approved for the indication of hyperuricemia associated with chemotherapy, allopurinol is acceptable as a comparator drug because the Japanese clinical guidance for treatment of TLS recommends allopurinol for patients at an intermediate or high risk (patients who are unable to take rasburicase) of TLS, and because allopurinol has been widely used in clinical practice in Japan. Although no apparent between-group differences were observed in the incidence of TLS or renal impairment-related events in clinical studies, there are limitations in evaluating such events on the basis of clinical study data. Therefore, post-marketing information on TLS and renal impairment should continue to be collected.

### 7.R.2 Safety

The applicant's explanation:
As shown in Table 3, there were no notable between-group differences in the incidence of adverse events in Japanese Study TMX-67TLS-01. Frequently reported adverse events included white blood cell (WBC) count decreased, constipation, nausea, neutrophil count decreased, and malaise, all of which are expected in patients undergoing chemotherapy and anticipated from the co-morbidities seen among the study population; a causal relationship to the study drug was ruled out for all these events.

Table 6 shows the incidence of febuxostat-related events of special interest[7)] (gouty arthritis, hepatic impairment-related events, hypersensitivity-related events, renal impairment-related events, cytopenia-related events, thyroid function-related events, cardiovascular events, and rhabdomyolysis-related events) identified on the basis of the Japanese clinical study data for initial approval and/or foreign safety information.

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5) Study FLO-01: A randomized, double-blind, allopurinol-controlled parallel-group comparative study was conducted in patients with hematologic malignancies (346 enrolled subjects) to evaluate the efficacy and safety of febuxostat for treatment of hyperuricemia associated with chemotherapy. Subjects were to receive orally febuxostat 120 mg qd or allopurinol 200 to 300 mg qd, or febuxostat 120 mg/day or allopurinol 600 mg/day twice daily. Subjects in the twice-daily febuxostat group received a dose of febuxostat 120 mg and a dose of placebo per day. Subjects received the treatment from 2 days prior to chemotherapy for malignant tumors for 7 days, and the treatment duration was allowed to be extended up to 9 days at the discretion of the investigator.

6) Defined as "an increase in serum creatinine by ≥0.3 mg/dL from baseline within 48 hours from the start of chemotherapy" or as "a ≥1.5-fold increase in serum creatinine from baseline to Day 6 of treatment with febuxostat" by referring to the definition of acute kidney injury described in "KDIGO Clinical Practice Guideline for Acute Kidney Injury" (translation supervised by the Japanese Society of Nephrology; Tokyo Igakusha Co., Ltd., 2014).

7) Consisting of gouty arthritis, hepatic impairment-related events, hypersensitivity-related events, renal impairment-related events, cytopenia-related events, thyroid function-related events, cardiovascular events, and rhabdomyolysis-related events defined by the applicant

**Table 6. Incidence of adverse events (Study TMX-67TLS-01, safety analysis set)**

| Event term | Febuxostat (N = 49) | Allopurinol (N = 50) |
|---|---|---|
| Overall adverse events | 93.9 (46) | 96.0 (48) |
| Overall adverse drug reactions | 2.0 (1) | 2.0 (1) |
| Serious adverse events | 0.0 (0) | 4.0 (2) |
| Adverse events leading to discontinuation | 0.0 (0) | 2.0 (1) |
| Grade 3/4[a)] adverse events | 77.6 (38) | 76.0 (38) |
| Gouty arthritis | 0.0 (0) | 2.0 (1) |
| Hepatic impairment-related events | 16.3 (8) | 20.0 (10) |
| Hypersensitivity-related events | 16.3 (8) | 22.0 (11) |
| Renal impairment-related events | 14.3 (7) | 8.0 (4) |
| Cytopenia-related events | 69.4 (34) | 72.0 (36) |
| Thyroid function-related events | 0.0 (0) | 0.0 (0) |
| Cardiovascular events | 6.1 (3) | 4.0 (2) |
| Rhabdomyolysis-related events | 2.0 (1) | 0.0 (0) |

Incidence % (n)

a) Determined by the investigator according to CTCAE v4.0-JCOG

The following events did not tend to occur at higher incidence in the febuxostat group than in the allopurinol group: hepatic impairment-related events, hypersensitivity-related events, and cytopenia-related events. In addition, thyroid function-related events were not reported in either group. Gouty arthritis, which has been known to be induced by a rapid fall in urate level caused by urate-lowering agents, was reported by only 1 subject in the allopurinol group and 0 subjects in the febuxostat group in Japanese Study TMX-67TLS-01. This subject had a history of gout and experienced gouty arthritis 9 days after the end of treatment with allopurinol. Renal impairment-related events were reported more frequently in the febuxostat group than in the allopurinol group, but all were nonserious and a causal relationship to the study drug was ruled out. In either group, cardiovascular events reported were nonserious and its causal relationship to the study drug was ruled out. Because foreign clinical studies of febuxostat conducted in gout patients suggested a trend towards a higher incidence of cardiovascular adverse events in the febuxostat group than that in the control group, foreign post-marketing clinical studies (Studies TMX-67_301[8)] and FUM005[9)]) are ongoing in order to elucidate the cardiovascular risk associated with febuxostat. One rhabdomyolysis-related event (blood creatine phosphokinase increased) was reported by 1 subject in the febuxostat group. The event was nonserious and a causal relationship to the study drug was ruled out.

The incidence of adverse events in foreign Study FLO-01 is shown in Table 7. Commonly reported adverse events included neutropenia, anaemia, leukopenia, thrombocytopenia, nausea, and pyrexia; of these, anaemia (22.5% in the febuxostat group, 14.5% in the allopurinol group) and pyrexia (13.9% and 10.4% in the respective groups) were reported at a higher incidence in the febuxostat group than in the allopurinol group. The incidence of adverse drug reactions was similar between the 2 groups, and all adverse drug reactions reported in the febuxostat group were mild or moderate in severity. A total of 6 deaths were reported in the febuxostat group (pneumonia/sepsis/septic shock, myocardial ischaemia/cardiac failure acute, haematuria/sepsis/shock, bronchitis, atrial fibrillation/pneumonia/renal failure,[10)] and febrile neutropenia/pneumonia/respiratory failure), but for all these deaths, a causal relationship to the study drug was ruled out for reasons including the following: most of these deaths occurred after the end of treatment with febuxostat; and they were considered attributed to primary disease or complications associated with chemotherapy. Serious adverse events were reported more frequently in the febuxostat group than in the allopurinol group, but a causal relationship to the study drug was ruled out for all events. Adverse events leading to treatment discontinuation (haematuria/sepsis/shock) were reported by 1 subject in the febuxostat group, but a causal relationship to the study drug was ruled out. Severe adverse events were reported more frequently in the febuxostat

8) Study TMX-67_301: A randomized, double-blind, allopurinol-controlled parallel-group comparative study in patients with gout at a high cardiovascular risk to evaluate the cardiovascular safety of febuxostat (target sample size, 7500 subjects). This study will evaluate the time to first occurrence of major MACE events (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or unstable angina associated with urgent revascularization) in patients treated with 40 to 80 mg/day of febuxostat or 200 to 600 mg/day of allopurinol (*Am Heart J.* 2012;164:14-20).

9) Study FUM005: A randomized, open-label, allopurinol-controlled parallel-group comparative study in patients with gout at a high cardiovascular risk to evaluate the cardiovascular safety of febuxostat (target sample size, 5706 subjects). This study will evaluate the time to first occurrence of events that are defined according to Antiplatelet Trialists' Collaboration (APTC) in patients treated with 80 to 120 mg/day of febuxostat or the optimal dose of allopurinol (*BMJ Open.* 2014;4:e005354).

10) This patient experienced recurrence of TLS and renal failure 6 days after the end of treatment with febuxostat and died 5 days later. The applicant explained that the renal failure and death were not attributed to lack of efficacy of febuxostat.

group than in the allopurinol group, but a causal relationship to the study drug was ruled out for many of these events. Adverse drug reactions were reported only by 2 subjects (cholestasis/hepatotoxicity and nausea) in the allopurinol group.

**Table 7. Incidence of adverse events (Study FLO-01, safety analysis set)**

| Event term | Febuxostat (N = 173) | Allopurinol (N = 173) |
|---|---|---|
| Overall adverse events | 67.6 (117) | 64.7 (112) |
| Overall adverse drug reactions | 6.4 (11) | 6.4 (11) |
| Deaths | 3.5 (6) | 0.0 (0) |
| Serious adverse events | 12.1 (21) | 3.5 (6) |
| Adverse events leading to discontinuation | 0.6 (1) | 0.0 (0) |
| Severe adverse events | 31.2 (54) | 18.5 (32) |
| Moderate adverse events | 41.0 (71) | 37.6 (65) |
| Mild adverse events | 56.6 (98) | 56.1 (97) |

Incidence % (n)

The above safety evaluation based on the Japanese and foreign clinical study data for patients with hyperuricemia associated with chemotherapy indicated no concerns about an increased risk with febuxostat as compared with allopurinol.

Serious adverse drug reactions in the Japanese post-marketing periodic safety update report[11)] data included gouty arthritis in 4 subjects, hepatic impairment-related events in 39 subjects, hypersensitivity-related events in 21 subjects, renal impairment-related events in 38 subjects, cytopenia-related events in 30 subjects, thyroid function-related event in 1 subject, cardiovascular events in 26 subjects, and rhabdomyolysis-related events in 8 subjects. However, at present, no new risks of specific concern have been identified. In addition, 11 fatal outcomes for which a causal relationship to febuxostat could not be ruled out (e.g., cerebral infarction, cardiac failure, ventricular arrhythmia, sudden cardiac death, renal failure chronic, and drug-induced liver injury) were reported during the period covered by the periodic safety update, but the relationship between these deaths and febuxostat was unclear because there were other possible factors such as underlining conditions, other suspect drugs, and/or concomitant drugs.

Given the Japanese and foreign clinical study data and post-marketing data, no additional precautionary statements regarding hyperuricemia associated with chemotherapy are required.

PMDA's view:
No clinically relevant differences in the safety were observed between the febuxostat and allopurinol groups in Japanese or foreign clinical studies, and no new clinically significant safety concerns were detected in the post-marketing data. Therefore, the safety of febuxostat is acceptable if the previously approved precautionary statement regarding the indication is provided.

### 7.R.3 Clinical positioning

The applicant's explanation:
Highly drug-sensitive tumors are generally known to grow rapidly, and by the time of diagnosis, a tumor burden is already high in many cases due to progression. A rapid lysis of tumor cells during chemotherapy leads to a massive release of intracellular materials including nucleic acids, potassium, phosphorus, and proteins into circulating blood, which may in turn cause TLS, characterized by hyperuricemia, electrolyte abnormality (such as hyperkalemia and hyperphosphatemia), renal disorder, and the resultant multi-organ failure. In particular, in patients with hyperuricemia associated with chemotherapy, decrease in urinary pH enhances formation of urate crystals in the renal tubules, and the deposited urate crystals may cause tubular obstruction leading to acute renal failure or death. For this reason, appropriate prophylaxis of TLS based on the development risk is critical, and that appropriate control of serum urate level is especially important in order to prevent TLS-related renal impairment including acute renal failure (Japanese clinical guidance for treatment of TLS).

The risk of TLS is eventually classified into categories of high, intermediate, and low according to disease risk classification adjusted based on renal function risk. Firstly, patients are classified as having high-risk disease (TLS incidence ≥5%), intermediate-risk disease (TLS incidence 1%-5%), or low-risk disease (TLS incidence <1%) based on the primary disease (e.g., solid tumors, multiple myeloma,

11) Patient exposure is estimated to be 2,556,526 patient-years.

leukemia, and malignant lymphoma), stage/type, WBC count, and lactate dehydrogenase (LDH) level, etc. Secondly, hematologic malignancy is classified as a high- to low-risk disease according to stage/type, WBC count, and LDH level, etc. TLS associated with solid tumors is considered less frequent than TLS associated with hematologic malignancies, and overall solid tumors are classified as low-risk diseases. However, tumors highly sensitive to chemotherapy such as neuroblastoma, small cell lung cancer, and germ cell tumor are classified as intermediate-risk diseases if the tumor burden is high. Lastly, high-risk diseases are categorized as diseases with a high risk of TLS, and intermediate- or low-risk diseases as those with a high to low risk depending on the final results of risk adjustment based on factors including renal function and serum urate level.

Conventional supportive care is fluid replacement given to all patients irrespective of the risk of TLS, and urate-lowering agents depending on the risk of TLS.

For patients at a high risk of TLS, massive fluid replacement followed by treatment with rasburicase (a urate-degrading enzyme) is recommended. Rasburicase has a potent urate-lowering activity and can decrease the urate level rapidly, but has been reported to induce neutralizing antibodies and cause serious allergic symptoms after retreatment in antibody-positive patients. Therefore, rasburicase cannot be used in patients who were previously treated with rasburicase in principle. In addition, the occurrence of haemolytic anaemia and methaemoglobinaemia was reported and rasburicase is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency. Consequently, uric acid production inhibitors are recommended for patients who are at a high risk of TLS and ineligible for rasburicase.

For patients at an intermediate risk of TLS, massive fluid replacement followed by treatment with a uric acid production inhibitor is recommended. However, rasburicase is recommended instead of uric acid production inhibitors for patients at an intermediate risk of TLS who require rapid reduction of serum urate level, such as those experiencing an abrupt rise in serum urate level after initiation of chemotherapy despite the use of uric acid production inhibitors or those with high urate levels at the time of diagnosis.

For patients at a low risk of TLS, conventional fluid replacement is recommended and urate-lowering agents are not for hyperuricemia; but for those with a trend towards an elevated serum urate level, those with a giant tumor, and/or those with an advanced and/or highly proliferative tumor, uric acid production inhibitors are recommended.

Nucleic acids released from tumor cells are metabolized to purines and converted to hypoxanthine, xanthine, and then to uric acid by xanthine oxidase, which is inhibited by allopurinol and febuxostat, i.e., uric acid production inhibitors. Although not yet approved for the indication of hyperuricemia associated with chemotherapy in Japan, allopurinol is recommended by the Japanese clinical guidance for treatment of TLS for patients at an intermediate risk of TLS, and is widely used in clinical practice in Japan. However, in patients with renal impairment, in whom blood levels of oxypurinol, an active metabolite of allopurinol, remain high due to the delay in excretion, dose reduction should be considered because of concerns about adverse drug reactions. In addition, patients receiving chemotherapy generally experience nausea/vomiting, and thus, allopurinol, requiring thrice-daily dosing, imposes a substantial burden on patients. Febuxostat requires only once-daily dosing, and can be used without dose adjustment in patients with mild or moderate renal impairment due to the limited contribution of renal metabolism.

Consequently, febuxostat, a uric acid production inhibitor, can provide a therapeutic option for patients with hyperuricemia associated with chemotherapy at different risk levels of developing TLS.

PMDA's view:
Febuxostat provides a therapeutic option for patients with hyperuricemia associated with chemotherapy because the non-inferiority of febuxostat over allopurinol was demonstrated in terms of the serum urate AUC [see "7.R.1 Efficacy"], and because no clinically relevant safety concerns have been observed [see "7.R.2 Safety"].

### 7.R.4 Indication

The applicant's explanation:
TLS frequently occurs in patients with hematologic malignancies including malignant lymphoma and acute leukemia. However, TLS may also be experienced by patients with solid tumors which have a high tumor burden, or are highly sensitive to chemotherapy, or who are receiving highly effective

therapeutic drugs such as molecular targeted drugs. The results of Japanese Study TMX-67TLS-01 in patients with hematologic malignancies and those with solid tumors showed no substantial difference in the serum urate AUC (primary endpoint) between the febuxostat and allopurinol groups in either patient population (Table 4). The incidence of adverse events by primary disease revealed no substantial difference among primary diseases between the febuxostat and allopurinol groups as follows: 100% (5 of 5 subjects) and 80.0% (4 of 5 subjects), respectively, in patients with leukemia; 90.9% (30 of 33 subjects) and 97.0% (32 of 33 subjects), respectively, in patients with lymphoma; and 100% (11 of 11 subjects) and 100% (12 of 12 subjects), respectively, in patients with solid tumors. Consequently, the intended patient population can include both patients with hematologic malignancies and those with solid tumors.

The intended patient population for febuxostat should be selected according to the latest information including the Japanese clinical guidance for treatment of TLS in consideration of the risk of TLS and characteristics of available drugs. Chemotherapy is expected to be provided individually by chemotherapy specialists at specialized medical centers who are versed in the risk of TLS and the latest treatment guidelines including recommended drugs. Therefore, proper patient selection can be ensured by including a precautionary statement that risk of TLS should be considered in the package insert.

Febuxostat, a uric acid production inhibitor, is expected to be effective in preventing renal impairment including TLS-related acute renal failure if used before initiation of chemotherapy to inhibit uric acid production and maintain the low serum urate levels until completion of chemotherapy. While rasburicase is indicated for "Hyperuricemia associated with cancer chemotherapy," febuxostat was proposed to be indicated for "Prevention of hyperuricemia associated with cancer chemotherapy" because febuxostat, unlike rasburicase, cannot directly degrade uric acid that is already formed.

PMDA asked the applicant to explain the appropriateness of having excluded patients with high baseline serum urate levels from Japanese Study TMX-67TLS-01, and also the necessity to include such patients in the intended patient population.

The applicant's response:
Japanese Study TMX-67TLS-01 excluded patients with baseline serum urate levels ≥10 mg/dL in order to secure subjects' safety. Patients with high serum urate levels before initiation of chemotherapy may have signs of TLS or already experience TLS resulting from spontaneous tumor lysis. For such patients requiring immediate management to rapidly reduce serum urate levels, febuxostat is not recommended because febuxostat, unlike rasburicase, cannot directly degrade circulating uric acid that is already formed. The Japanese clinical guidance for treatment of TLS includes a description to the effect that use of rasburicase should be considered in patients with persistent urate elevation despite prophylaxis with allopurinol or febuxostat or patients showing hyperuricemia already at the time of diagnosis although no consensus has been reached; therefore, treatment with rasburicase should be considered in patients with high baseline serum urate levels.

PMDA's view:
The efficacy and safety of febuxostat in patients with hyperuricemia associated with chemotherapy were similar between patients with hematologic malignancies and those with solid tumors [see "7.R.1 Efficacy"] in Japanese Study TMX-67TLS-01, and there is no particular problem with including the both patient groups in the intended patient population. Physicians should be advised that candidates for treatment with febuxostat need to be selected according to the latest information including the Japanese clinical guidance for treatment of TLS in consideration of the risk of TLS, etc. "Prevention of" is unnecessary in the description of the proposed indication "Prevention of hyperuricemia associated with cancer chemotherapy," since proper use of febuxostat can be ensured by appropriately stating dose timing and that febuxostat cannot directly degrade uric acid. The appropriateness of descriptions in the package insert regarding indication will be finalized, taking account of comments raised in the Expert Discussion.

### 7.R.5 Dosage and administration

The applicant's explanation:
Japanese phase II exploratory study (Study TMX-67-[redacted]) was conducted, before the initial approval, to support the indication of febuxostat "gout and hyperuricemia" and the mean percent change in serum

urate level from baseline to Week 16 was -36.6% in the allopurinol 300 mg/day group, -43.0% in the febuxostat 40 mg/day group, and -52.5% in the febuxostat 60 mg/day group. Comparison of efficacy of the maintenance dose between allopurinol 300 mg/day (thrice daily) and febuxostat 40 or 60 mg/day (once daily) revealed that the efficacy was comparable between the febuxostat 40 mg and allopurinol 300 mg groups, and that treatment with febuxostat 60 mg achieved greater rate of decrease than treatment with allopurinol 300 mg.

Urate-lowering agents have been known to induce gouty arthritis through a rapid fall in urate level, and for the treatment of gout and hyperuricemia, the initially approved indication, febuxostat is recommended to be administered in a dose escalation regimen. The risk of gouty arthritis has been considered to depend upon the degree and duration of serum urate elevation, and in patients with gout/hyperuricemia, prolonged high serum urate levels induce deposition of urate crystals in the joints, leading to gouty arthritis (The Japanese Society of Gout and Nucleic Acid Metabolism eds. *Guideline for the Management of Hyperuricemia and Gout*, 2nd ed. [in Japanese]. Medical Review Co., Ltd.; 2010).

Unlike patients with gout/hyperuricemia, patients with malignant tumors who develop hyperuricemia associated with chemotherapy (the intended patient population for this application) do not generally exhibit prolonged high serum urate levels and are unlikely to suffer from deposition of urate crystals in the joints, and therefore, have only a low risk of gouty arthritis. In addition, a Japanese phase I study (Study TMX-67-[redacted]) conducted to support the indication of febuxostat "gout and hyperuricemia" demonstrated tolerability of 7-day oral administration of febuxostat ≤160 mg qd with no dose escalation in healthy adult male subjects. Thus, the risk of gouty arthritis is limited in patients with hyperuricemia associated with chemotherapy and there are limited safety concerns associated with febuxostat administered at an initial dose of 60 mg; therefore, there is no need to use a dose escalation scheme.

Based on the above, in Japanese Study TMX-67TLS-01 conducted in patients with hyperuricemia associated with chemotherapy, febuxostat and allopurinol were administered at the maximum doses previously approved (febuxostat 60 mg/day, allopurinol 300 mg/day [or 200 mg/day depending on the patient's clinical condition]), not in a dose escalation scheme, in order to achieve adequate reduction in serum urate levels. As a result, the non-inferiority of febuxostat over allopurinol was demonstrated in terms of the serum urate AUC from baseline to Day 6 (primary endpoint). There was no difference in the safety between the allopurinol and febuxostat groups in Japanese Study TMX-67TLS-01 as well, and gouty arthritis was not reported in the febuxostat group.

In Japanese Study TMX-67TLS-01, treatment with febuxostat was started at 24 hours (acceptable range, ± 4 hours) prior to initiation of chemotherapy according to the TLS panel consensus. The Japanese clinical guidance for treatment of TLS recommends that uric acid production inhibitors be administered from 1 to 2 days prior to chemotherapy. However, in clinical settings, since there is less urgency in initiating chemotherapy for solid tumor patients and in order to more reliably prevent TLS through urate control, urate-lowering agents are occasionally administered from several days prior to initiation of chemotherapy. Therefore, it is appropriate to start treatment ≥1 day prior to initiation of chemotherapy, rather than a fixed time for starting.

In general, TLS has been reported to develop commonly after 12 to 72 hours of chemotherapy administration (*J Clin Oncol*. 2008;26:2767-2778, *Br J Haematol*. 2010;149:578-586). In addition, patients with solid tumors, unlike those with hematologic malignancies, have been reported to develop TLS at various timings, between ≤24 hours and several days to weeks, after chemotherapy depending on cell cycle or sensitivity to chemotherapy (*Clin Oncol*. 2006;18:773-780). Therefore, in Japanese Study TMX-67TLS-01, which was designed to cover at least 12 to 72 hours after initiation of chemotherapy with febuxostat treatment, patients were to receive study treatment for 6 days (until 5 days into chemotherapy) and were allowed to receive for up to 14 days depending on the primary disease, type of chemotherapy, and patient's condition. As a result, 3 of 49 patients in the febuxostat group and 6 of 50 patients in the allopurinol group received the study drug for >6 days. All 3 patients who received the study drug for >6 days in the febuxostat group were to receive chemotherapy on or after Day 6 of febuxostat treatment. These patients included one with diffuse large B-cell lymphoma determined to be at a high risk of TLS, who received febuxostat for 13 days; another with diffuse large B-cell lymphoma determined to be at a high risk of TLS, who received febuxostat for 10 days; and the other with small cell lung cancer determined to be at a high risk of TLS, who received febuxostat for 14 days.

Consequently, in patients with hyperuricemia associated with chemotherapy, febuxostat 60 mg qd should be administered with no dose escalation. In addition, precautionary statements should be included in the Precautions for Dosage and Administration section of the package insert to the effect that treatment should be started ≥1 day prior to initiation of chemotherapy and continued until 5 days into chemotherapy in principle, and that the treatment should be extended as necessary depending on the patient's condition, instead of strictly specifying the maximum duration of treatment or its start timing.

PMDA's view:
There is no particular problem with the proposed dosage regimen of febuxostat 60 mg qd administered orally with no dose escalation. Timing of starting treatment with febuxostat should be specified as 1 to 2 days prior to chemotherapy because Japanese Study TMX-67TLS-01, in which treatment with febuxostat was started at 24 hours prior to chemotherapy, demonstrated non-inferiority of febuxostat over allopurinol in terms of the serum urate AUC, and the Japanese clinical guidance for treatment of TLS recommends that treatment be started 1 to 2 days prior to chemotherapy. In Japanese Study TMX-67TLS-01, subjects were to receive study treatment until 5 days into chemotherapy in principle, and were allowed to receive for up to 14 days depending on their condition. Although only limited number of patients received febuxostat after 5 days into chemotherapy in Japanese Study TMX-67TLS-01, there is no particular problem with administering febuxostat until 5 days into chemotherapy in principle or with extending treatment duration on an as-needed basis while monitoring the patient's serum urate level depending on the patient's condition, given the long-term safety of febuxostat used for the approved indication. The appropriateness of the dosage and administration, timing of starting treatment, and treatment duration will be finalized, taking account of comments raised in the Expert Discussion.

### 7.R.6 Special patient populations

#### 7.R.6.1 Patients with renal impairment

The applicant's explanation:
The incidence of adverse events by renal function in Japanese Study TMX-67TLS-01 is shown in Table 8. No substantial between-group difference by renal function was observed in the incidence of adverse events or adverse drug reactions. The incidence of renal impairment-related events and cytopenia-related events tended to increase with decreasing renal function in the febuxostat group, but a similar trend was observed in the allopurinol group for cytopenia-related events. Renal impairment-related events reported in the febuxostat group included blood urea increased in 3 subjects, renal impairment in 2 subjects, and chromaturia and pollakiuria in 1 subject each; all these events were nonserious and a causal relationship to the study drug was ruled out. Because the clinical studies excluded patients with eGFR <30 mL/min/1.73 $m^2$, febuxostat should be carefully administered in patients with severe renal impairment while closely monitoring the patient's condition when used in patients with hyperuricemia associated with chemotherapy, as is the case for the approved indication (gout and hyperuricemia). Among febuxostat-related events of special interest, gouty arthritis, thyroid function-related events, cardiovascular events, and rhabdomyolysis-related events were infrequently reported overall, and therefore, it was difficult to discuss the safety by renal function.

**Table 8. Incidence of adverse events by renal function (Study TMX-67TLS-01, safety analysis set)**

| | Febuxostat | | | | Allopurinol | | | |
|---|---|---|---|---|---|---|---|---|
| eGFR (mL/min/1.73 $m^2$) | <45 | ≥45 to <60 | ≥60 to <90 | ≥90 | <45 | ≥45 to <60 | ≥60 to <90 | ≥90 |
| Overall adverse events | 100.0 (1/1) | 100.0 (10/10) | 93.3 (28/30) | 87.5 (7/8) | 100.0 (3/3) | 100.0 (13/13) | 92.0 (23/25) | 100.0 (9/9) |
| Overall adverse drug reactions | 0.0 (0/1) | 0.0 (0/10) | 3.3 (1/30) | 0.0 (0/8) | 0.0 (0/3) | 0.0 (0/13) | 4.0 (1/25) | 0.0 (0/9) |
| Hepatic impairment-related events | 0.0 (0/1) | 10.0 (1/10) | 16.7 (5/30) | 25.0 (2/8) | 33.3 (1/3) | 23.1 (3/13) | 16.0 (4/25) | 22.2 (2/9) |
| Hypersensitivity-related events | 0.0 (0/1) | 10.0 (1/10) | 16.7 (5/30) | 25.0 (2/8) | 0.0 (0/3) | 30.8 (4/13) | 28.0 (7/25) | 0.0 (0/9) |
| Renal impairment-related events | 0.0 (0/1) | 20.0 (2/10) | 13.3 (4/30) | 12.5 (1/8) | 0.0 (0/3) | 7.7 (1/13) | 12.0 (3/25) | 0.0 (0/9) |
| Cytopenia-related events | 100.0 (1/1) | 80.0 (8/10) | 70.0 (21/30) | 50.0 (4/8) | 66.7 (2/3) | 92.3 (12/13) | 72.0 (18/25) | 44.4 (4/9) |

Incidence % (number of subjects with the event/number of subjects included in the analysis)

The Japanese post-marketing periodic safety update report showed no particular trend in the incidence of serious adverse drug reactions in patients with severe renal impairment (eGFR <30 mL/min/1.73 $m^2$). In foreign post-marketing safety information, a tendency was found for the incidence of renal impairment-related events to be higher in patients with renal impairment (with a history of conditions classified under the system organ class (SOC) “renal and urinary disorders”), but no other notable trend in the incidence of adverse events was observed.

PMDA’s view:
Given the incidence of adverse events by renal function in Japanese clinical studies, there are no significant problems with the safety in patients with renal impairment of moderate or lower severity. However, the clinical studies excluded patients with severe renal impairment, thus, febuxostat should be used with care in patients with severe renal impairment, as is the case for the approved indication, and post-marketing information on the safety in patients with renal impairment should continue to be collected.

### 7.R.6.2 Patients with hepatic impairment

The applicant’s explanation:
The incidence of adverse events in Japanese Study TMX-67TLS-01 is shown in Table 9 by the presence or absence of liver function abnormality. Although evaluation was limited by the small number of subjects with liver function abnormality, the incidence of hepatic impairment-related events, renal impairment-related events, and cytopenia-related events tended to be higher in subjects with liver function abnormality than in those without liver function abnormality among subjects in the febuxostat group. Adverse events such as WBC count decreased, decreased appetite, nausea, and neutrophil count decreased were reported by 6 subjects complicated with hepatic dysfunction (alcoholic cirrhosis, gallstone, cholecystolithiasis, or hepatic impairment). All events were nonserious and a causal relationship to the study drug was ruled out. The clinical studies excluded patients with AST or ALT levels >3 times the ULN, thus, febuxostat should be carefully administered in patients with hepatic impairment while closely monitoring the patient’s condition when used in patients with hyperuricemia associated with chemotherapy, as is the case for the approved indication (gout and hyperuricemia). Among febuxostat-related events of special interest, gouty arthritis, thyroid function-related events, cardiovascular events, and rhabdomyolysis-related events were infrequently reported overall, and therefore, it was difficult to discuss the safety by the presence or absence of liver function abnormality.

**Table 9. Incidence of adverse events by the presence or absence of liver function abnormality (Study TMX-67TLS-01, safety analysis set)**

| | Febuxostat | | Allopurinol | |
|---|---|---|---|---|
| Liver function abnormality[a)] | Yes | No | Yes | No |
| Overall adverse events | 100.0 (8/8) | 92.7 (38/41) | 100.0 (8/8) | 95.2 (40/42) |
| Overall adverse drug reactions | 12.5 (1/8) | 0.0 (0/41) | 0.0 (0/8) | 2.4 (1/42) |
| Hepatic impairment-related events | 37.5 (3/8) | 12.2 (5/41) | 12.5 (1/8) | 21.4 (9/42) |
| Hypersensitivity-related events | 12.5 (1/8) | 17.1 (7/41) | 25.0 (2/8) | 21.4 (9/42) |
| Renal impairment-related events | 25.0 (2/8) | 12.2 (5/41) | 0.0 (0/8) | 9.5 (4/42) |
| Cytopenia-related events | 87.5 (7/8) | 65.9 (27/41) | 62.5 (5/8) | 73.8 (31/42) |

Incidence % (number of subjects with the event/number of subjects included in the analysis)
a) Patients with liver function abnormality were defined as those with baseline AST or ALT levels greater than the ULN.

The Japanese post-marketing periodic safety update report showed no particular trend in the incidence of serious adverse drug reactions in patients with liver function abnormality (patients with AST or ALT levels ≥50 U/L). In foreign post-marketing safety information, the incidence of hepatic impairment-related events tended to be higher in patients with hepatic impairment (patients with a history of conditions classified under the SOC "hepatobiliary disorders"), but no other notable trend was observed in the incidence of adverse events.

PMDA's view:
Although evaluation was limited by the small number of subjects with liver function abnormality, hepatic impairment-related events were frequently reported in the subgroup of subjects with liver function abnormality among subjects in the febuxostat group in Japanese clinical studies. In addition, the clinical studies excluded patients with AST or ALT levels >3 times the ULN. Therefore, febuxostat should be used with care in patients with hepatic impairment, as is the case for the approved indication, and post-marketing information on the safety in patients with hepatic impairment should continue to be collected.

### 7.R.6.3 Elderly patients

The incidence of adverse events in Japanese Study TMX-67TLS-01 is shown by age group in Table 10. No substantial between-group difference was observed in the incidence of adverse events or adverse drug reactions either between elderly patients or between non-elderly patients. In the febuxostat group, the incidence of renal impairment-related events, hepatic impairment-related events, and hypersensitivity-related events tended to be higher among elderly patients than among non-elderly patients, but a similar trend was observed in the allopurinol group for renal impairment-related events. Hepatic impairment-related events reported by elderly patients in the febuxostat group included hepatic function abnormal in 3 subjects; and ALT increased/AST increased, γ-glutamyltransferase increased, and blood alkaline phosphatase increased in 1 subject each. The events of ALT increased/AST increased were assessed as adverse drug reactions, but were nonserious and Grade 1 in severity. All the other hepatic impairment-related events were nonserious and a causal relationship to the study drug was ruled out. Hypersensitivity-related events reported by elderly patients in the febuxostat group included stomatitis in 2 subjects; and eczema, erythema, flushing, rash, and urticaria in 1 subject each. All these events were nonserious and a causal relationship to the study drug was ruled out. Among febuxostat-related events of special interest, gouty arthritis, thyroid function-related events, cardiovascular events, and rhabdomyolysis-related events were infrequently reported overall, and therefore, it was difficult to discuss the safety by age group.

**Table 10. Incidence of adverse events by age group (Study TMX-67TLS-01, safety analysis set)**

| | Febuxostat | | Allopurinol | |
|---|---|---|---|---|
| Age | ≥65 years | <65 years | ≥65 years | <65 years |
| Overall adverse events | 93.1 (27/29) | 95.0 (19/20) | 94.4 (34/36) | 100.0 (14/14) |
| Overall adverse drug reactions | 3.4 (1/29) | 0.0 (0/20) | 2.8 (1/36) | 0.0 (0/14) |
| Hepatic impairment-related events | 20.7 (6/29) | 10.0 (2/20) | 19.4 (7/36) | 21.4 (3/14) |
| Hypersensitivity-related events | 20.7 (6/29) | 10.0 (2/20) | 22.2 (8/36) | 21.4 (3/14) |
| Renal impairment-related events | 20.7 (6/29) | 5.0 (1/20) | 11.1 (4/36) | 0.0 (0/14) |
| Cytopenia-related events | 72.4 (21/29) | 65.0 (13/20) | 75.0 (27/36) | 64.3 (9/14) |

Incidence % (number of subjects with the event/number of subjects included in the analysis)

No particular trends were observed in the incidence of serious adverse drug reactions in elderly patients in the Japanese post-marketing periodic safety update report or in foreign post-marketing safety information.

PMDA's view:
On the basis of the incidence of adverse events by age group in Japanese clinical studies, there is no particular concern about the safety in elderly patients. However, patients should be closely monitored for clinical conditions and caution should be exercised when febuxostat is administered to elderly patients, who generally have reduced physiological function and may suffer from rapid decline in renal function. In addition, information on the safety in elderly patients should continue to be collected via post-marketing surveillance.

### 7.R.7 Post-marketing investigations

The applicant's explanation:
In order to evaluate the efficacy and safety of febuxostat in patients with hyperuricemia associated with chemotherapy in routine clinical practice, a use-results survey with a sample size of 300 patients will be conducted. Each patient will be observed from the start of treatment with febuxostat until the first visit occurring ≥3 days after the last dose of febuxostat. This survey will investigate occurrences of hepatic impairment, hypersensitivity, renal impairment, cytopenia, cardiovascular events, thyroid function-related events, and rhabdomyolysis, etc.

PMDA's view:
In addition to the evaluation to be conducted by the applicant, information on the safety in patients with renal or hepatic impairment should be collected. Details of post-marketing surveillance will be finalized, taking account of comments raised in the Expert Discussion.

## 8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

### 8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The assessment is ongoing. Its results and the conclusion by PMDA will be described in the Review Report (2).

### 8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The inspection is ongoing. Its results and the conclusion by PMDA will be described in the Review Report (2).

## 9. Overall Evaluation during Preparation of the Review Report (1)

PMDA has concluded that the data submitted demonstrate the efficacy of febuxostat in the treatment of patients with hyperuricemia associated with cancer chemotherapy and acceptable safety in view of the benefits indicated by the data submitted. Febuxostat, as a uric acid production inhibitor, offers a therapeutic option for patients with hyperuricemia associated with cancer chemotherapy. Occurrences of hepatic impairment, hypersensitivity, renal impairment, cytopenia, cardiovascular events, thyroid function-related events, and rhabdomyolysis, and the safety in patients with renal or hepatic impairment, etc. should be further investigated after the market launch.

PMDA has concluded that febuxostat may be approved if febuxostat is not considered to have any particular problems based on comments from the Expert Discussion.

**Review Report (2)**

April 4, 2016

**Product Submitted for Registration**

| | |
|---|---|
| **Brand Name** | Feburic Tablets 10 mg<br>Feburic Tablets 20 mg<br>Feburic Tablets 40 mg |
| **Non-proprietary Name** | Febuxostat |
| **Applicant** | Teijin Pharma Limited |
| **Date of Application** | July 29, 2015 |

## 1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized in the following. The expert advisors present during the Expert Discussion were nominated based on their declarations etc., concerning the product submitted for marketing approval, 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).

### 1.1 Efficacy

PMDA's view:

In Japanese Study TMX-67TLS-01, the non-inferiority of Feburic over allopurinol was demonstrated in terms of the area under the serum urate AUC from baseline to Day 6, the primary endpoint. Therefore, PMDA concluded that the efficacy of Feburic in patients with hyperuricemia associated with chemotherapy has been demonstrated. Although the comparator drug allopurinol has not been approved for the indication of hyperuricemia associated with chemotherapy, allopurinol is acceptable as a comparator drug because the Japanese Society of Medical Oncology ed. *Japanese clinical guidance for treatment of Tumor Lysis Syndrome (TLS)* [in Japanese]. Kanehara & Co., Ltd.; 2013 (the Japanese clinical guidance for treatment of TLS) recommends allopurinol for patients at an intermediate or high risk (patients who are unable to take Rasburicase [Genetical Recombination]) of TLS, and because allopurinol has been widely used in clinical practice in Japan. Although no apparent between-group differences were observed in the incidence of TLS or renal impairment-related events in clinical studies, since there are limitations in evaluating such events based on clinical study data, post-marketing information on occurrences of TLS and renal impairment-related events should continue to be collected.

This conclusion was supported by the expert advisors.

### 1.2 Safety

PMDA's view:

No clinically relevant differences in the safety were observed between the febuxostat and allopurinol groups in Japanese Study TMX-67TLS-01 or foreign phase III Study FLO-01. No new clinically significant safety concerns were detected in the post-marketing data. Therefore, the safety of febuxostat is acceptable if the precautionary statement regarding the indication previously approved for Feburic is provided.

This conclusion was supported by the expert advisors.

### 1.3 Indication

PMDA's view:

The efficacy and safety of febuxostat in patients with hyperuricemia associated with cancer chemotherapy were similar between patients with hematologic malignancies and those with solid tumors in Japanese Study TMX-67TLS-01, thus, there is no particular problem with including the both patient groups in the intended patient population. Physicians should be advised that candidates for treatment with febuxostat need to be selected according to the latest information including the Japanese clinical

guidance for treatment of TLS in consideration the risk of TLS, etc. Regarding the description of the proposed indication of "Prevention of hyperuricemia associated with cancer chemotherapy," the words "Prevention of" are unnecessary since proper use of febuxostat can be ensured by stating appropriate timing of dosing in the Precautions for Dosage and Administration section, and stating the fact that febuxostat cannot directly degrade uric acid in the Precautions for Indications section of the package insert.

This conclusion was supported by the expert advisors. The expert advisors commented that since febuxostat is expected to be used in patients including those already having hyperuricemia in clinical practice, the descriptions "Prevention of" should not be included.

Based on the above, PMDA requested the applicant to modify the text in the Indication section to "Hyperuricemia associated with cancer chemotherapy," and confirmed that appropriate actions have been taken.

### 1.4 Dosage and administration

PMDA's view:

There is no particular problem with the proposed dosage and administration of febuxostat 60 mg qd administered orally with no dose escalation. Treatment with febuxostat should be started 1 to 2 days prior to chemotherapy because Japanese Study TMX-67TLS-01, in which treatment with febuxostat was started at 24 hours prior to chemotherapy, demonstrated non-inferiority of febuxostat over allopurinol in terms of the serum urate AUC, and the Japanese clinical guidance for treatment of TLS recommends that treatment be started 1 to 2 days prior to chemotherapy. In Japanese Study TMX-67TLS-01, subjects were to receive study treatment until 5 days into chemotherapy in principle, and were allowed to receive for up to 14 days depending on their condition. Although only limited number of patients received febuxostat after 5 days into chemotherapy in Japanese Study TMX-67TLS-01, there is no particular problem with administering febuxostat until 5 days into chemotherapy in principle or with extending treatment duration on an as-needed basis while monitoring the patient's serum urate level depending on the patient's condition, given that the long-term safety of febuxostat has been demonstrated for the previously approved indication.

This conclusion was supported by the expert advisors. The following comments were raised from expert advisors:

- Patients with acute leukemia, malignant lymphoma, or multiple myeloma may undergo chemotherapy consisting of a >5-day course of antineoplastic drugs or may receive once- or twice-a-week treatment, and it can be difficult to specify a fixed treatment duration of febuxostat.

- TLS may develop 10 days to 2 weeks after initiation of chemotherapy.

- Therefore, it is important that treatment duration can be extended on an as-needed basis while the patient's serum urate level is monitored, depending on the patient's condition.

Based on the above, PMDA requested the applicant to modify the text in the Precautions for Dosage and Administration section as shown below, and confirmed that appropriate actions have been taken.

**Precautions for Dosage and Administration**

(1) Feburic treatment should be started 1 to 2 days prior to initiation of cancer chemotherapy.

(2) Feburic should be administered until 5 days into cancer chemotherapy while the patient's clinical symptoms and blood urate level are monitored. Treatment should be extended as necessary depending on the patient's condition.

### 1.5 Draft risk management plan

Taking account of the review in the "7.R.7 Post-marketing investigations" section of the Review Report (1) and the comments from the expert advisors at the Expert Discussion, PMDA concluded that the applicant should additionally investigate the following points through post-marketing surveillance:

- Safety in patients with renal or hepatic impairment

PMDA instructed the applicant to investigate it through post-marketing surveillance.

The applicant agreed to the above instruction.

Taking account of the above discussion, PMDA has concluded that, at present, the risk management plan (draft) for Feburic should include the safety and efficacy specifications listed in Table 11 and additional pharmacovigilance and risk minimization activities listed in Table 12.

**Table 11. Safety and efficacy specifications in the risk management plan (draft)**

| Safety specification | | |
|---|---|---|
| Important identified risks | Important potential risks | Important missing information |
| • Hepatic impairment<br>• Hypersensitivity<br>• Gouty arthritis (for indication of gout and hyperuricemia) | • Renal impairment<br>• Blood disorders (e.g., platelet count decreased, white blood cell count decreased)<br>• Cardiovascular events<br>• Thyroid function-related events<br>• Rhabdomyolysis | • Safety in patients with hepatic impairment<br>• Safety in patients with renal impairment |
| Efficacy specification | | |
| • Use-results survey (indication of hyperuricemia associated with cancer chemotherapy)<br>• Specified use-results survey (long-term treatment) (indication of gout and hyperuricemia)[a)] | | |

a) Ongoing

**Table 12. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)**

| Additional pharmacovigilance activities | Additional risk minimization activities |
|---|---|
| • Early post-marketing phase vigilance (indication of hyperuricemia associated with cancer chemotherapy)<br>• Use-results survey (indication of hyperuricemia associated with cancer chemotherapy)<br>• Specified use-results survey (long-term treatment) (indication of gout and hyperuricemia)[a)] | • Early post-marketing phase vigilance (indication of hyperuricemia associated with cancer chemotherapy)<br>• Preparation and provision of materials for health-care providers (indication of hyperuricemia associated with cancer chemotherapy) |

a) Ongoing

**Table 13. Outline of use-results survey plan (draft)**

| | |
|---|---|
| Objective | To investigate the efficacy and safety of Feburic in clinical use for indication of hyperuricemia associated with cancer chemotherapy |
| Survey method | Central registration |
| Population | Patients who received Feburic for treatment of hyperuricemia associated with cancer chemotherapy |
| Observation period | From the day of treatment initiation with Feburic until the first visit occurred ≥7 days after the last dose of Feburic (last observation date) in principle |
| Planned sample size | 300 patients |
| Main survey items | Patient characteristics, use status of Feburic, chemotherapy regimen, prior medication used for treatment of hyperuricemia associated with cancer chemotherapy, concomitant medication/concomitant therapy, adverse events, laboratory values, incidence of TLS, etc. |

## 2. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

### 2.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. PMDA thus concluded that there were no obstacles to conducting its review based on the application documents submitted.

### 2.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (5.3.5.1-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. As a

result, PMDA concluded that the clinical studies as a whole have been conducted in compliance with GCP and that there were no obstacles to conducting its review based on the application documents submitted. The inspection revealed the following findings at some study sites, which did not significantly affect the overall evaluation of the study, and notified to the head of the study sites as matters to be improved.

**Matters to be improved**

Study sites

- Written informed consent was not obtained from some subjects before they participated in the study.*

* Of these, 1 subject was excluded from all analyses presented in this application because of deviations in the written informed consent. This case was handled as a GCP violation while the application documents were being developed.

## 3. Overall Evaluation

As a result of the above review, PMDA has concluded that Feburic may be approved after modifying the previously approved Indication, and Dosage and Administration as shown below, with the following conditions. Since this application has been submitted seeking approval of a drug with a new indication/dosage, the appropriate re-examination period applied to the indication and dosage and administration below should be 4 years.

**Indication**

1. Gout and hyperuricemia
2. Hyperuricemia associated with cancer chemotherapy

(Underline denotes additions.)

**Dosage and administration**

1. Gout and hyperuricemia

The usual initial adult dosage is febuxostat 10 mg administered orally once daily. Then, the dose should be gradually increased, as necessary, with blood urate levels monitored. 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.

2. Hyperuricemia associated with cancer chemotherapy

The usual adult dosage is febuxostat 60 mg administered orally once daily.

(Underline denotes additions.)

**Conditions of approval**

The applicant is required to develop and appropriately implement a risk management plan.