Long-Term Safety and Effectiveness of the Xanthine Oxidoreductase Inhibitor, Topiroxostat in Japanese Hyperuricemic Patients with or Without Gout: A 54-week Open-label, Multicenter, Post-marketing Observational Study

Tomohiko Ishikawa1 · Tatsushi Maeda2 · Teruo Hashimoto3 · Tetsuya Nakagawa2 · Kazuhito Ichikawa2 · Yasushi Sato4 · Yoshihiko Kanno5

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Abstract

Background and Objectives Topiroxostat, a selective xanthine oxidoreductase inhibitor, is used for the management of hyperuricemic patients with or without gout in Japan. Accumulating evidence has demonstrated the efficacy of topiroxostat for the treatment of hyperuricemia with or without gout. However, the safety and efficacy of topiroxostat in the clinical setting remain unclear, and there is little large-scale clinical evidence. We conducted a post-marketing observational study over 54 weeks.

Patients and Methods Patients were centrally enrolled, and case report forms of 4491 patients were collected between April 2014 and March 2019 from 825 medical sites.

Results Overall, 4329 patients were assessed for safety and 4253 patients for effectiveness. The overall incidence of adverse drug reactions was 6.95%, and the incidence rates of adverse drug reactions of gouty arthritis, hepatic dysfunction, and skin disorders, which are of special interest in this study, were 0.79%, 1.73%, and 0.95%, respectively. No case of serious gouty arthritis was observed. Serum urate levels decreased stably over time and showed a significant reduction rate at 54 weeks (21.19% ± 22.07%) and on the final visit (19.91% ± 23.35%) compared to the baseline. The rates for subjects who achieved serum uric acid levels ≤ 6.0 mg/dL at 18 and 54 weeks after administration were 43.80% and 48.28%, respectively.

Conclusions This study suggests that there is no particular concern about adverse drug reactions or the efficacy of topiroxostat for hyperuricemic patients with or without gout in a post-marketing setting in Japan.

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Key Points

The safety and efficacy of the novel non-purine selective xanthine oxidoreductase inhibitor, topiroxostat, were investigated over 54 weeks in a post-marketing study.

There were no new findings that would raise questions about the safety of topiroxostat under actual conditions of use, and its efficacy was shown to be the same as clinical studies had reported at the time of approval.

Topiroxostat is considered a safe and effective drug for gout and hyperuricemia in daily practice.
1 Introduction

Hyperuricemia (defined as a serum urate level > 7.0 mg/dL in Japan) is a causative factor for urate deposition diseases such as urolithiasis and gouty arthritis [1]. Defects in single and multiple genes have been suggested as the cause of hyperuricemia. These reportedly affect nucleic acid metabolism-related enzymes that promote uric acid production or urate transporters that reduce renal excretion of uric acid [2, 3]. Hyperuricemia is broadly divided into the overproduction of uric acid, the underexcretion of it, and mixed types. Recently, the existence of a renal load type, including reduced extrarenal excretion of uric acid and the overproduction of uric acid and reduced extrarenal excretion, has also been proposed [2]. Three urate transporters, URAT1/SLC22A12, GLUT9/SLC2A9, and ABCG2/BCRP, are reported to play crucial roles in the regulation of serum urate level, and their dysfunction causes urate transport disorders (hypouricemia and/or hyperuricemia). ABCG2 variants have been shown to have stronger effects on the risk of hyperuricemia/gout than major environmental risk factors such as obesity and heavy drinking [4].

Reducing serum urate levels and maintaining it at or below 6.0 mg/dL is a major target in treating hyperuricemia to prevent gouty arthritis [5–8]. Drugs that reduce serum uric acid levels are roughly classified into two types: uric acid synthesis inhibitors that inhibit xanthine oxidoreductase (XOR) and uric acid excretion accelerators that inhibit renal uric acid reabsorption. Topiroxostat, (Topiloric® tablets and Uriadec® tablets) a non-purine selective XOR inhibitor, belongs to the group of uric acid synthesis inhibitors. It is a hybrid inhibitor that inhibits enzyme activity by covalent binding with molybdenum and by interaction with amino acid residues in the substrate-binding pocket [9, 10].

There have been several reports on the safety and efficacy of topiroxostat, mainly in development trials, and topiroxostat not only reduces serum uric acid levels [11–13] but also may have a possible positive effect on renal function [14–17].

We report here the results of a post-marketing study conducted to collect information on the safety, efficacy, and proper use of topiroxostat.

2 Patients and Methods

2.1 Study Design

This was a prospective, observational, multicenter post-marketing study carried out in routine clinical practice, and co-sponsored by the manufacturers to investigate the safety and effectiveness of topiroxostat (Topiloric®, Fuji Yakuhin Co., Ltd., Saitama, Japan) and Uriadec® (Sanwa Kagaku Kenyusho Co., Ltd., Aichi, Japan). The study was carried out in accordance with the Good Post-Marketing Study Practice standards specified by the Ministry of Health, Labor and Welfare in Japan.

2.2 Participants and Data Assessment

Patients were recruited from medical institutions throughout Japan and were enrolled using a central registration system from April 2014 to 31 March 2017. Each patient was followed up for 54 weeks from the date of first topiroxostat administration, using Electronic Data Capture.

This study collected patient background information, such as age, gender, BMI, reasons for using this drug, disease duration of gout or hyperuricemia, and concomitant disease.

Safety was assessed according to the incidence of adverse drug reactions (ADRs), the change in clinical laboratory tests of aspartate transaminase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (γ-GTP), total bilirubin, and triglycerides, as well as total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, blood urea nitrogen (BUN), serum creatinine (Cr), and hemoglobin A1c (HbA1c). Urinalysis (protein and occult blood) was performed, and blood pressure, pulse, body weight, estimated glomerular filtration rate (eGFR) and urinary albumin/Cr ratio were documented. Furthermore, the incidence of cardiovascular adverse events and ADRs from renal and urinary tract disorders were also tabulated.

Efficacy endpoints were changes in serum uric acid levels, a decrease rate of serum uric acid levels at 18 weeks and 54 weeks after administration and at the final evaluation, and the achievement rate of ≤ 6 mg/dL.

Priority research factors include gouty arthritis, hepatic dysfunction, skin disorders, and safety and efficacy in special patient subgroups. These included the elderly, females, and patients with hepatic or renal dysfunction.

2.3 Statistical Analysis

The subgroup analysis of the incidence of ADRs by patient background factors and the special patient subgroups were tested using the Chi square test or Fisher’s exact test, and the analysis of changes in clinical test values was performed using the one-sample t test. A level of less than 5% (two-sided) was considered significant. Adverse events (AEs) and ADRs were categorized according to the Medical Dictionary for Regulatory Activities/Japanese edition (MedDRA/J) version 22.0. Changes in serum uric acid levels and decrease
rates were analyzed using one-sample $t$ tests, and subgroup analysis of serum uric acid decrease rates in specific patient populations was performed by analysis of variance.

2.4 Trial Registration

This PMS study was retrospectively registered on Japic-Clinical Trials Information as JapicCTI-173783 on November 22, 2017.

3 Results

3.1 Patient Disposition and Characteristics

Figure 1 shows the patient disposition in the study. In total, 4642 patients were registered at 825 medical sites across Japan. With the exception of 151 cases for which the case report form (CRF) could not be collected, 4491 CRFs (18 weeks) and 3657 CRFs (54 weeks) were collected and fixed.

Of the 4491 cases, 162 were excluded owing to the absence of visits after enrollment ($n=158$), duplicate registration ($n=3$), and lack of exposure to the drug ($n=1$), leaving 4329 patients for the safety analyses. An additional 76 patients were excluded from the effectiveness analyses, (73—no effectiveness data available, 2—prior use of topiroxostat, 1 off-label use), leaving 4253 patients.

Table 1 summarizes the baseline characteristics of the 4329 safety analysis subjects in this study. The mean serum uric acid level was 8.11 ± 1.46 mg/dL, and the number of cases with a serum uric acid level of 7.0 mg/dL or more was 3436 (79.37%).

The details of specific patient populations (elderly, female, hepatic dysfunction, renal dysfunction) were as follows: there were 2364 (54.61%) elderly people aged ≥ 65, and 1238 (28.60%) aged > 75. There were 851 (19.66%) female patients, 434 (10.03%) hepatic dysfunction patients, 3469 (80.13%) patients with renal dysfunction.

3.2 Usage Status of this Drug

The average daily dose of the 4329 patients subject to safety analysis was 50.57 mg/day. The dose escalation was 794 cases (18.34%), and the one-step dose escalation was the highest in 638 cases (14.74%).

Of the 4329 safety analysis subjects in this study, 3203 (73.99%) completed use for one year (54 weeks), and 1126 (26.01%) discontinued or dropped out. The main reasons for discontinuation or withdrawal included no visit [365 cases (8.43%)], AEs [198 cases (4.57%)], the achievement of the treatment purpose [115 cases (2.66%)], change of hospital [104 cases (2.40%)], or failure to collect the CRF by the end of the survey due to the lack of cooperation of a doctor [199 cases (4.60%)].

3.3 Safety Results

ADRs reported by attending physicians are summarized in Table 2. All observed ADRs are listed in the Table S2. In 4329 cases subject to safety analysis, 390 ADRs occurred in 301 cases, and the overall incidence of ADRs was 6.95%, which was lower than the 35.35% (292/826) incidence of ADRs in clinical trials up to the time of approval.

The main ADRs were abnormal hepatic function ($n=39$, 0.90%), gouty arthritis ($n=34$, 0.79%), pruritus and renal impairment ($n=15$, 0.35% each), and liver disorders ($n=12$, 0.28%).

Table 3 shows the incidence of ADRs by patient background factors. Background factors with a high incidence of ADRs included history of gouty arthritis, gout nodules, and concomitant disease (renal disease, cardiovascular disease, hypertension), with a significant difference compared to the absence of each. In addition, there was a significant difference in the incidence of ADRs in the presence or absence of gradual increased dosing, the total number of days of administration, and the total dose.

3.3.1 Changes in Clinical Test Values

Serum creatinine tended to increase after 10 weeks’ administration, and a significant difference was observed compared to the start of administration after 30 weeks’ administration, but the mean change after 54 weeks was a slight increase of 0.066, BUN did not show an increasing trend. The renal dysfunction patients (eGFR < 90 mL/min/1.73 m²: 80.13%) and the elderly (aged ≥ 65 years, 54.61%) were more likely to be affected by the natural history of these patients. Although there were also significant differences in ALT, ALP, γ-GTP, total bilirubin, triglycerides (TG), total cholesterol, HDL cholesterol, LDL cholesterol, BUN, eGFR, HbA1c, blood pressure (systolic, diastolic) and body weight, the fluctuation range was small or it was not a change for the worse.

Fig. 1 Patient disposition. CRF case report form
Table 1  Patient baseline characteristics of safety analysis subjects (N=4329)

| Characteristics                                      | Value                                                                 |
|-------------------------------------------------------|----------------------------------------------------------------------|
| Age (years)                                           | 64.1 ± 15.2; 66.0 (13–103)                                          |
| < 65                                                  | 1965 (45.39)                                                         |
| 65 to < 75                                            | 1126 (26.01)                                                         |
| ≥ 75                                                  | 1238 (28.60)                                                         |
| Gender                                                |                                                                      |
| Male                                                  | 3478 (80.34)                                                         |
| Female                                                | 851 (19.66)                                                          |
| BMI (kg/m²) [n = 3250]                                |                                                                      |
| < 18.5                                                | 119 (2.75)                                                           |
| 18.5 to < 25                                          | 1613 (37.26)                                                         |
| 25 to < 30                                            | 1151 (26.59)                                                         |
| 30 to < 35                                            | 279 (6.44)                                                           |
| 35 to < 40                                            | 70 (1.62)                                                            |
| ≥ 40                                                  | 18 (0.42)                                                            |
| Unknown                                               | 1079 (24.92)                                                         |
| Reason (including double counts)                      |                                                                      |
| Gout                                                  | 728 (16.82)                                                          |
| Hyperuricemia                                         | 3974 (91.80)                                                         |
| Others                                                | 8 (0.18)                                                             |
| Disease duration of gout or hyperuricemia (years)     |                                                                      |
| < 5                                                   | 2005 (46.32)                                                         |
| 5 to < 10                                             | 527 (12.17)                                                          |
| ≥10                                                  | 348 (8.04)                                                           |
| Unknown                                               | 1449 (33.47)                                                         |
| History of gouty arthritis                            | 663 (15.32)                                                          |
| Gout nodules                                           | 86 (1.99)                                                            |
| Disease classification a                              |                                                                      |
| Overproduction                                        | 427 (9.86)                                                           |
| Underexcretion                                        | 365 (8.43)                                                           |
| Mixed                                                 | 279 (6.44)                                                           |
| Normal                                                | 34 (0.79)                                                            |
| Not evaluated                                         | 3224 (74.47)                                                         |
| Concomitant disease                                   | 3819 (88.22)                                                         |
| Liver disease                                         | 1319 (30.47)                                                         |
| Renal disease                                         | 1868 (43.15)                                                         |
| Hemodialysis                                          | 91 (2.10)                                                            |
| Cardiovascular disease                                | 846 (19.54)                                                          |
| Hypertension                                          | 2720 (62.83)                                                         |
| Hyperlipidemia (dyslipidemia)                         | 2213 (51.12)                                                         |
| Diabetes                                              | 1112 (25.69)                                                         |
| Others                                                | 1339 (30.93)                                                         |
| Usual alcohol drinker                                 | 1866 (43.10)                                                         |
| Serum uric acid at start (mg/dL) [N = 4014]           | 8.11 ± 1.46; 8.10 (1.4–1.3)                                          |
| < 6.0                                                 | 318 (7.35)                                                           |
| 6.0 to < 7.0                                          | 260 (6.01)                                                           |
| 7.0 to < 8.0                                          | 1070 (24.72)                                                         |
| 8.0 to < 9.0                                          | 1440 (33.26)                                                         |
| 9.0 to < 10.0                                         | 605 (13.98)                                                          |
| ≥10.0                                                 | 321 (7.42)                                                           |
| Unknown                                               | 315 (7.28)                                                           |
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3.3.2  Key Safety Research Items

The ADRs of gouty arthritis, hepatic dysfunction, and skin disorders were examined as research items with special interest.

In 4329 safety analysis cases, the incidence rates of ADRs of gouty arthritis, hepatic dysfunction, and skin disorders were 0.79% (34 cases), 1.73% (75 cases) and 0.95% (41 cases), respectively (Table 4). No serious gouty arthritis was observed. One case each of serious hepatic dysfunction, hepatic cirrhosis, and liver disorder occurred. There was one case each of serious skin disorder, drug eruption, and urticaria. In skin disorders, in terms of the onset period, 19 cases occurred within 42 days or fewer, and 22 cases occurred on a total dose of less than 2500 mg. The incidence was high in the early stage of administration.

3.3.3  Safety in Special Patient Populations

The incidence of ADRs is shown in elderly patients, female patients, and patients with hepatic or renal dysfunction (Table 3). Such patients have not been sufficiently studied because of the small numbers in reported clinical trials. In the stratified analysis by age, gender, and hepatic or renal function, no significant difference was found in the incidence of ADRs in any of the subgroups.

3.3.4  Other Analysis Items

Cardiovascular AEs The AE rate of cardiovascular events was 0.79% (34/4329 cases) (Table 5). There were no significant changes in the relevant laboratory test values (TG, total cholesterol, HDL cholesterol, LDL cholesterol, or in blood pressure, and pulse).

ADRs of renal and urinary tract disorders The incidence of ADRs of renal and urinary tract disorders was 0.16% (7/4329 cases), of which five were presence of blood urine and one was urinary calculus and hemorrhagic cystitis (Table 5).

3.4  Efficacy

Changes in the serum uric acid level during the administration of topiroxostat are shown in Fig. 2, and the rate of decrease of serum uric acid levels are shown in Table 6. In 4253 patients subject to efficacy analysis, the mean value of serum uric acid at the start of administration was 8.11 ± 1.46 mg/dL (4014 cases), the mean value after 18 weeks was 6.35 ± 1.47 mg/dL (2744 cases). The mean value after 54 weeks was 6.14 ± 1.31 mg/dL (2274 cases). In addition, the average value at the final evaluation, including the discontinuation of administration and the end of administration, was 6.31 ± 1.46 mg/dL (3935 cases).
The decrease rate of serum uric acid level was 19.03% ± 23.90% (2639 cases) after 18 weeks, 21.19% ± 22.07% (2191 cases) after 54 weeks, and 19.91% ± 23.35% (3706 cases) at the time of final evaluation, all showed a significant decrease compared to the start of administration.

The achievement rate of serum uric acid level of 6.0 mg/dL or less was 43.80% (1202/2744 cases) after 18 weeks, 48.28% (1098/2274 cases) after 54 weeks, and 44.55% (1753/3935 cases) at the final evaluation (Table 7). In addition, the achievement rate of 6.0 mg/dL or less in patients whose serum uric acid level exceeded 6.0 mg/dL at the start of administration was 41.87% (1004/2398 cases) after 18 weeks, and 46.05% (914/1985 cases) after 54 weeks, and 42.39% (1434/3383 cases) at the time of final evaluation (Table 7).

We examined the rate of decrease in serum uric acid levels in elderly patients, female patients, and hepatic or renal dysfunction patients. The same decrease was observed as in non-elderly patients, and patients without hepatic or renal dysfunction. Gender stratification analysis, however, showed that females had significantly higher reduction rates than males (Table 8).

### Table 2  Incidence of adverse drug reactions observed in ≥3 patients

| Preferred term                                      | n (%) |
|-----------------------------------------------------|-------|
| No. of patients analyzed                            | 4329  |
| No. of patients with ADRs                           | 301   |
| Incidence of ADRs                                   | 6.95% |
| Hepatic function abnormal                           | 39 (0.90%) |
| Gouty arthritis                                     | 34 (0.79%) |
| Pruritus                                            | 15 (0.35%) |
| Renal impairment                                    | 15 (0.35%) |
| Liver disorder                                      | 12 (0.28%) |
| Rash                                                | 8 (0.18%) |
| Blood triglycerides increased                       | 8 (0.18%) |
| Hypertriglyceridemia                                | 7 (0.16%) |
| Drug eruption                                       | 7 (0.16%) |
| Alanine aminotransferase increased                  | 7 (0.16%) |
| Blood creatinine increased                          | 7 (0.16%) |
| Blood urea increased                                | 7 (0.16%) |
| Diarrhea                                            | 6 (0.14%) |
| Protein urine present                               | 6 (0.14%) |
| Hyperlipidemia                                      | 5 (0.12%) |
| Blood pressure increased                            | 5 (0.12%) |
| Gamma-glutamyl-transferase increased                | 5 (0.12%) |
| Blood urine present                                 | 5 (0.12%) |
| Aspartate aminotransferase increased                | 4 (0.09%) |
| Pneumonia                                           | 3 (0.07%) |
| Iron deficiency anemia                              | 3 (0.07%) |
| Diabetes mellitus                                   | 3 (0.07%) |
| Hypertension                                        | 3 (0.07%) |
| Gastro-esophageal reflux disease                    | 3 (0.07%) |
| Nausea                                              | 3 (0.07%) |
| Malaise                                             | 3 (0.07%) |
| Low-density lipoprotein increased                   | 3 (0.07%) |
| Blood alkaline phosphatase increased                | 3 (0.07%) |

ADR adverse drug reaction
MedDRA/J version (22.0)

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4 Discussion

The safety and efficacy of topiroxostat under daily use were confirmed by this 54-week post-marketing study. In general, randomized controlled trials can provide the highest levels of clinical evidence with the least bias but cannot collect all data relevant to use in routine clinical practice. Therefore,
### Table 3  Incidence of adverse drug reactions by patients’ background factors

| Patient characteristics | Category | No. of patients | No. of patients with ADRs (%) | No of ADRs | Statistics |
|-------------------------|----------|----------------|------------------------------|------------|------------|
| Total                   |          | 4329           | 301 (6.95)                   | 390        |            |
| Age (years)             | <65      | 1965           | 131 (6.67)                   | 177        | \(p=0.1216\) |
|                         | 65 to <75| 1126           | 69 (6.13)                    | 88         |            |
|                         | \(\geq 75\) | 1238         | 101 (8.16)                   | 125        |            |
| Gender                  | Male     | 3478           | 233 (6.70)                   | 300        | \(p=0.2009\) |
|                         | Female   | 851            | 68 (7.99)                    | 90         |            |
| BMI [kg/m²]             | <18.5    | 119            | 13 (10.92)                   | 16         | \(p=0.2294\) |
|                         | 18.5 to <25 | 1613        | 142 (8.80)                   | 186        |            |
|                         | 25 to <30 | 1151           | 79 (6.86)                    | 99         |            |
|                         | 30 to <35 | 279            | 22 (7.89)                    | 33         |            |
|                         | 35 to <40 | 70             | 4 (5.71)                     | 5          |            |
|                         | \(\geq 40\) | 18            | 0 (0.00)                     | 0          |            |
|                         | Unknown  | 1079           | 41 (3.80)                    | 51         |            |
| Reason (including double counts) | Gout     | 728            | 59 (8.10)                    | 79         |            |
|                         | Hyperuricemia | 3974       | 277 (6.97)                   | 356        |            |
|                         | Others   | 8              | 0 (0.00)                     | 0          |            |
| Disease duration of gout or hyperuricemia (years) | <5      | 2005           | 127 (6.33)                   | 159        | \(p=0.3993\) |
|                         | 5 to <10  | 527            | 39 (7.40)                    | 54         |            |
|                         | \(\geq 10\) | 348        | 28 (8.05)                    | 33         |            |
|                         | Unknown  | 1449           | 107 (7.38)                   | 144        |            |
| History of gouty arthritis | No    | 3666           | 235 (6.41)                   | 298        | \(p=0.0016\) |
|                         | Yes      | 663            | 66 (9.95)                    | 92         |            |
| Gout nodules            | No       | 4243           | 289 (6.81)                   | 370        | \(p=0.0168\) |
|                         | Yes      | 86             | 12 (13.95)                   | 20         |            |
| Disease classification  | Overproduction type | 427  | 22 (5.15) | 25 \(p=0.4502\) |
|                         | Underexcretion type | 365 | 23 (6.30) | 31    |
|                         | Mixed    | 279            | 17 (6.09)                    | 24         |            |
|                         | Normal   | 34             | 0 (0.00)                     | 0          |            |
|                         | Not evaluated | 3224       | 239 (7.41)                   | 310        |            |
| Concomitant disease     | No       | 510            | 15 (2.94)                    | 16         | \(p<0.0001\) |
|                         | Yes      | 3819           | 286 (7.49)                   | 374        |            |
| Liver disease           | No       | 3010           | 199 (6.61)                   | 252        | \(p=0.1941\) |
|                         | Yes      | 1319           | 102 (7.73)                   | 138        |            |
| Renal disease           | No       | 2461           | 135 (5.49)                   | 175        | \(p<0.0001\) |
|                         | Yes      | 1868           | 166 (8.89)                   | 215        |            |
| Hemodialysis            | No       | 4238           | 297 (7.01)                   | 385        | \(p=0.4099\) |
|                         | Yes      | 91             | 4 (4.40)                     | 5          |            |
| Cardiovascular disease  | No       | 3483           | 219 (6.29)                   | 280        | \(p=0.0009\) |
|                         | Yes      | 846            | 82 (9.69)                    | 110        |            |
| Hypertension            | No       | 1609           | 91 (5.66)                    | 115        | \(p=0.0094\) |
|                         | Yes      | 2720           | 210 (7.72)                   | 275        |            |
| Hyperlipidemia (dyslipidemia) | No    | 2116           | 137 (6.47)                   | 168        | \(p=0.2324\) |
|                         | Yes      | 2213           | 164 (7.41)                   | 222        |            |
| Diabetes                | No       | 3217           | 229 (7.12)                   | 299        | \(p=0.4945\) |
|                         | Yes      | 1112           | 72 (6.47)                    | 91         |            |
| Others                  | No       | 2990           | 163 (5.45)                   | 200        | \(p<0.0001\) |
|                         | Yes      | 1339           | 138 (10.31)                  | 190        |            |
Table 3 (continued)

| Patient characteristics | Category | No. of patients | No. of patients with ADRs (%) | No of ADRs | Statistics |
|-------------------------|----------|----------------|------------------------------|-----------|------------|
| Usual alcohol drinker   | No       | 1828           | 119 (6.51)                  | 146       | \(q = 0.7916\) |
|                         | Yes      | 1866           | 126 (6.75)                  | 176       |            |
|                         | Unknown  | 635            | 56 (8.82)                   | 68        |            |
| Serum uric acid at baseline [mg/dL] | <6.0 | 318            | 21 (6.60)                   | 28        | \(q = 0.7160\) |
|                         | 6.0 to <7.0 | 260          | 18 (6.92)                   | 29        |            |
|                         | 7.0 to <8.0 | 1070          | 72 (6.73)                   | 102       |            |
|                         | 8.0 to <9.0 | 1440          | 101 (7.01)                  | 124       |            |
|                         | 9.0 to <10.0 | 605           | 45 (7.44)                   | 52        |            |
|                         | \(\geq 10.0\) | 321           | 30 (9.35)                   | 39        |            |
|                         | Unknown  | 315            | 14 (4.44)                   | 16        |            |
| Hepatic dysfunction (baseline AST, ALT [U/L])\(^b\) Severity | No (AST < 50 and ALT < 50) | 3137 | 238 (7.59) | 315 | \(q = 0.4665\) |
|                         | Mild (AST 50 to < 100 or ALT 50 to < 100) | 360 | 28 (7.78) | 35 |            |
|                         | Moderate (AST 100 to < 500 or ALT 100 to < 500) | 72 | 2 (2.78) | 2 |            |
|                         | Severe (AST \(\geq 500\) or ALT \(\geq 500\)) | 2 | 0 (0.00) | 0 |            |
|                         | Unknown  | 758            | 33 (4.35)                   | 38        |            |
| Renal dysfunction (baseline eGFR [mL/min/1.73 m\(^2\)])\(^b\) Severity | No (\(\geq 90\)) | 257 | 19 (7.39) | 24 | \(q = 0.1127\) |
|                         | Mild (60 to <90) | 1359 | 83 (6.11) | 105 |            |
|                         | Moderate (30 to <60) | 1551 | 133 (8.58) | 181 |            |
|                         | Severe (15 to <30) | 356 | 29 (8.15) | 31 |            |
|                         | End stage renal failure (<15) | 203 | 19 (9.36) | 29 |            |
|                         | Unknown  | 603            | 18 (2.99)                   | 20        |            |
| Gradual increase       | No       | 3535           | 220 (6.22)                  | 283       | \(q = 0.0001\) |
| Incremental phase       | Yes      | 794            | 81 (10.20)                  | 107       |            |
|                         | No       | 3535           | 220 (6.22)                  | 283       | \(q < 0.0001\) |
|                         | Once     | 638            | 58 (9.09)                   | 74        |            |
|                         | Twice    | 139            | 20 (14.39)                  | 29        |            |
|                         | 3 times  | 17             | 3 (17.65)                   | 4         |            |
| Average single dose [mg/time] | <10 | 0 | 0 – | 0 | \(q = 0.7660\) |
|                         | 10 to <20 | 16 | 1 (6.25) | 1 |            |
|                         | 20 to <40 | 3157 | 210 (6.65) | 270 |            |
|                         | 40 to <60 | 1004 | 79 (7.87) | 107 |            |
|                         | 60 to <80 | 120 | 9 (7.50) | 10 |            |
|                         | 80 to <120 | 32 | 2 (6.25) | 2 |            |
|                         | \(\geq 120\) | 0 | 0 – | 0 |            |
| Average daily dose [mg/day] | <10 | 0 | 0 – | 0 | \(q = 0.4172\) |
|                         | 10 to <20 | 8 | 0 (0.00) | 0 |            |
|                         | 20 to <40 | 638 | 39 (6.11) | 49 |            |
|                         | 40 to <60 | 2568 | 161 (6.52) | 200 |            |
|                         | 60 to <80 | 412 | 32 (7.77) | 46 |            |
|                         | 80 to <120 | 682 | 59 (8.65) | 84 |            |
|                         | 120 to <160 | 89 | 8 (8.99) | 9 |            |
|                         | 160 to <240 | 32 | 2 (6.25) | 2 |            |
|                         | \(\geq 240\) | 0 | 0 – | 0 |            |
the present study is important because it provides feedback on the use of topiroxostat in routine clinical practice.

As for the safety profile, the incidence of ADRs with topiroxostat was 6.95% in this study, indicating a lower rate compared with the aggregated results (35.35%) in the pre-approval trials. As priority items related to safety, we investigated the incidence of ADRs of gouty arthritis, hepatic dysfunction and skin disorders, and safety in the elderly, and in patients with hepatic or renal dysfunction, and in female patients. No problematic events were observed in the subgroups.

The prevalence of gout is estimated to be over 1% in men aged > 30 years and is still on the rise [18]. In addition, the occurrence of side effects of gouty arthritis associated with the treatment of hyperuricemia has become a problem. In this study, the incidence of gouty arthritis was 0.79% (34 of 4329 patients), with no serious cases, and was lower than that seen at the time of approval of 10.05% (83/826 patients). These results suggest that topiroxostat is a useful drug for patients with gout and hyperuricemia with a low incidence of gouty arthritis even when lowering serum uric acid levels.

It has been suggested that since topiroxostat is not affected by mild-to-moderate renal dysfunction, adjustment of dosage and administration is not required for these patients [14], and this study confirmed that there was no significant difference in the incidence of ADRs according to the severity of eGFR at the baseline.

As a result of examining the incidence of ADRs by patient background factors, when the total number of administration days was less than 14 and the total dose was less than 2500 mg, the incidence of ADRs was high; however, the effect of patients who discontinued the drug due to the appearance of side effects in the early stage of administration was considered.

Although there was a significant difference in the incidence rate of ADRs by some patient background factors, the tendency of the occurrence of ADRs did not differ. Further,
Table 4  Incidence of adverse drug reactions of special interest

| Special interest | ADR (PT) | Incidence (n = 4329) |
|------------------|----------|----------------------|
| Gouty arthritis*  | Total    | 34 (0.79)            |
|                  | Gouty arthritis | 34 (0.79) |
|                  | Gouty tophus   | 1 (0.02)            |
|                  | Gout          | 0 (−)               |
| Hepatic dysfunction*  | Total | 75 (1.73%)          |
|                    | Chronic hepatitis | 1 (0.02) |
|                    | Hepatic cirrhosis | 1 (0.02) |
|                    | Hepatic function abnormal | 39 (0.90) |
|                    | Hepatic steatosis | 2 (0.05) |
|                    | Hyperbilirubinemia | 1 (0.02) |
|                    | Liver disorder | 12 (0.28)           |
|                    | ALT abnormal   | 1 (0.02)            |
|                    | ALT increased  | 7 (0.16)            |
|                    | AST abnormal   | 1 (0.02)            |
|                    | AST increased  | 4 (0.09)            |
|                    | Blood bilirubin increased | 1 (0.02) |
|                    | GGTP abnormal  | 1 (0.02)            |
|                    | GGTP increased | 5 (0.12)           |
|                    | Transaminases increased | 1 (0.02) |
|                    | Blood ALP increased | 3 (0.07) |
|                    | Hepatic enzyme increased | 1 (0.02) |
| Skin disorders*  | Total    | 41 (0.95%)          |
|                  | Alopecia    | 1 (0.02)            |
|                  | Drug eruption | 7 (0.16)          |
|                  | Eczema       | 2 (0.05)            |
|                  | Erythema     | 2 (0.05)            |
|                  | Pruritus      | 15 (0.35)           |
|                  | Rash         | 8 (0.18)            |
|                  | Rash generalized | 2 (0.05) |
|                  | Rash pruritic | 1 (0.02)           |
|                  | Urticaria     | 2 (0.05)            |
|                  | Pruritus generalized | 1 (0.02) |
|                  | Toxic skin eruption | 2 (0.05) |

Values are expressed as n (%)

MedDRA/J version (22.0)

ADR adverse drug reaction, ALT alanine transaminase, AST aspartate transaminase, ALP alkaline phosphatase, GGTP gamma-glutamyl transpeptidase, MedDRA Medical dictionary for regulatory activities, PT preferred term, SMQ standardized MedDRA queries, SOC symptoms of the organ classification

*Extract the following as side effects of gouty arthritis, PT: gouty arthritis, gouty tophus, gout

**Extract the following as side effects of hepatic dysfunction, PT that fall under “hepato-biliary disorders of the Organ Classification (SOC)” and “SMQ liver-related laboratory tests, signs and Symptoms of the Organ Classification (SOC)”

*Extract the following as side effects of skin disorders, PT classified into skin and subcutaneous tissue disorders in the SOC

Table 5  Incidence of AEs/ADRs of other analysis items

| Item                  | PT                  | Incidence (n = 4329) |
|-----------------------|---------------------|----------------------|
| CV events*            | Total               | 34 (0.79%)          |
|                      | Brain stem infarction | 1 (0.02) |
|                      | Cerebral artery embolism | 1 (0.02) |
|                      | Cerebral hemorrhage  | 3 (0.07)            |
|                      | Cerebral infarction  | 11 (0.25)           |
|                      | Embolic stroke       | 1 (0.02)            |
|                      | Subarachnoid hemorrhage | 1 (0.02) |
|                      | Vertebral artery stenosis | 1 (0.02) |
|                      | Thrombotic cerebral infarction | 1 (0.02) |
|                      | Acute myocardial infarction | 3 (0.07) |
|                      | Angina pectoris      | 1 (0.02)            |
|                      | Arteriosclerosis coronary artery | 1 (0.02) |
|                      | Coronary artery disease | 1 (0.02) |
|                      | Myocardial ischemia  | 1 (0.02)            |
|                      | Acute coronary syndrome | 2 (0.05)  |
|                      | Subdural hematoma    | 5 (0.12)            |
|                      | Subdural hemorrhage  | 1 (0.02)            |
|                      | Total                | 7 (0.16%)           |
|                      | Calculus urinary     | 1 (0.02)            |
|                      | Cystitis hemorrhagic | 1 (0.02)            |
|                      | Blood urine present  | 5 (0.12)            |

Values are expressed as n (%)

MedDRA/J version (22.0)

ADR adverse drug reaction, AE adverse reaction (include events for which a causal relationship has been denied), CV cardiovascular, PT preferred term

*Extract the following as AEs of cardiovascular events

Severe basic terms (PT) classified as SMQ “Ischemic heart disease” and “CNS bleeding and cerebrovascular disease”

**Extract the following as ADRs of renal and urinary tract disorders

Preferred terms: ureterolithiasis, calculus urinary, cystitis hemorrhagic, hematuria, nephrolithiasis, blood urine present, red blood cells urine positive

Fig. 2  Changes in serum uric acid levels over time. Values are expressed as mean ± SD. *p < 0.0001 (one-sample t test). SD standard deviation

△ Adis
the rate of ADRs is not remarkably high compared with the overall incidence of ADRs at 6.95% (301/4329 cases).

The incidence of cardiovascular AEs was 0.79%, and of renal and urinary tract disorders was 0.16%, indicating no particular effect on safety.

Regarding efficacy, the reduction rate of serum uric acid level at the end of treatment in clinical trials (long-term administration study at 58 weeks) was 38.44% ± 13.34% (121 patients), and the achievement rate of ≤ 6.0 mg/dL was 70.0% (77/110 subjects) after 18 weeks, and 71.9% (87/121 subjects) at the end of administration; results of this study were all lower. In clinical trials, all cases were escalated to a maintenance dose of 120 or 160 mg/day, but the average daily dose in this study under actual conditions of use was < 60 mg/day: 71.93% (3114/4329 cases), which was thought to be because the low-dose cases accounted for the majority, and the escalating cases were as low as 18.34% (794/4329 cases). Based on these results, it is considered desirable to continue increasing the dose of topiroxostat in the necessary cases.

In this study, the rate of achievement of serum uric acid level of ≤ 6.0 mg/dL or less was lower than in reported clinical trials. However, a significant decrease in serum uric acid level was observed, compared to the start of treatment, and approximately half of the patients had a serum uric acid level of ≤ 6.0 mg/dL at 54 weeks after administration. A decrease in serum uric acid levels was also observed in specific patient populations, demonstrating the efficacy of topiroxostat under actual conditions of use.

Since the urate transporter is greatly involved in the regulation of serum uric acid level, it is also interesting to observe whether XOR inhibitors affect the function of urate transporters, such as URAT1, GLUT9 and ABCG2. ABCG2 variants have been shown to have stronger effects on the risk of hyperuricemia/gout than major environmental risk factors such as obesity and heavy drinking [4]. The most common dysfunction variant rs2231142 (p.Q141K), and the prevalent variant in Japan rs72552713 (p.Q126X), as well as rare variants, increase the risk of gout and hyperuricemia, significantly influence the age of onset of gout, and are highly associated with a familial gout history. The ABCG2 dysfunction was reported as a strong independent risk for pediatric-onset hyperuricemia/gout [19]. Moreover, a significant association between rs2231142 and an increased risk of a poor response to allopurinol has been described [20]. It might be very beneficial to include these common dysfunctional ABCG2 variants in any future study about topiroxostat treatment.

### Table 6 Percentage decrease in serum uric acid level from baseline at each time point

| Time point | Reduction rate of serum uric acid level [%] | One-sample t test |
|------------|-------------------------------------------|------------------|
|            | n  | Mean ± SD | Minimum | Median | Maximum |                  |
| 18 weeks   | 2639 | 19.03 ± 23.90 | −185.71 | 22.73  | 73.08   | $p < 0.0001$       |
| 54 weeks   | 2191 | 21.19 ± 22.07 | −167.50 | 23.75  | 81.08   | $p < 0.0001$       |
| Final visit | 3706 | 19.91 ± 23.35 | −185.71 | 22.75  | 81.08   | $p < 0.0001$       |

SD standard deviation

a Cases with test values at the start of administration and at each time after administration were included

b Regardless of the timing, the laboratory values at the time of the final measurement of each case were used

| Time point | Over all | Serum uric acid level at the start of administration exceeds 6.0 mg/dL | Achieving rate (%) |
|------------|----------|---------------------------------------------------------------|-------------------|
|            | n       | Achieving rate (%)                                           | Achieving rate (%) |
| 18 weeks   | 1202/2744 | 43.80 | 1004/2398 | 41.87 |
| 54 weeks   | 1098/2274 | 48.28 | 914/1985 | 46.05 |
| Final visit | 1753/3935 | 44.55 | 1434/3383 | 42.39 |

*a Cases with test values at each time after administration were included

*b Cases with test values at the start of administration and at each time after administration were included

*c Regardless of the timing, the laboratory values at the time of the final measurement of each case were used

In addition, we examined the rate of decrease in serum uric acid levels in elderly and female patients, and in patients with hepatic or renal dysfunction, where the number of cases in previous clinical trials has been too small to perform subgroup analyses. Concerning elderly patients and hepatic or renal dysfunction patients, there was no significant difference in the rate of decreases in serum uric acid levels compared to the general study population. Female patients had a higher decrease in serum uric acid levels than males.

Since the urate transporter is greatly involved in the regulation of serum uric acid level, it is also interesting to observe whether XOR inhibitors affect the function of urate transporters, such as URAT1, GLUT9 and ABCG2. ABCG2 variants have been shown to have stronger effects on the risk of hyperuricemia/gout than major environmental risk factors such as obesity and heavy drinking [4]. The most common dysfunction variant rs2231142 (p.Q141K), and the prevalent variant in Japan rs72552713 (p.Q126X), as well as rare variants, increase the risk of gout and hyperuricemia, significantly influence the age of onset of gout, and are highly associated with a familial gout history. The ABCG2 dysfunction was reported as a strong independent risk for pediatric-onset hyperuricemia/gout [19]. Moreover, a significant association between rs2231142 and an increased risk of a poor response to allopurinol has been described [20]. It might be very beneficial to include these common dysfunctional ABCG2 variants in any future study about topiroxostat treatment.
Conclusions

As a result of the study under actual conditions of use, there were no new findings that would raise questions about the safety of topiroxostat, and the efficacy of this drug was shown to be the same as had been reported in clinical studies at the time of approval. Therefore, topiroxostat is considered to be a safe and effective drug for gout and hyperuricemia in daily practice.

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Compliance with Ethical Standards

Conflict of interest YK is a medical advisor of Fuji Yakuhin Co., Ltd., and received consultant fees. TI, TH and YS are employees of Fuji Yakuhin Co., Ltd., TM, TN and KI are employees of Sanwa Kagaku Kenkyusho Co., Ltd.

Table 8 Percentile reduction in serum uric acid levels in a special patient population

| Background Category | Time after administration |
|---------------------|---------------------------|
|                     | 18 weeks | Analysis of variance | 54 weeks | Analysis of variance |
|                     | n   | Percentile reduction (mean %) | n   | Percentile reduction (mean %) |
| Total               | 2639 | 19.03 | – | 2191 | 21.19 | – |
| Age (years)         |       |       |       |       |
| <65                 | 1151 | 18.33 | \( p = 0.0007 \) | 934  | 21.01 | \( p = 0.3343 \) |
| 65 to <75           | 711  | 17.25 |          | 603  | 20.40 |          |
| ≥75                 | 777  | 21.68 |          | 654  | 22.19 |          |
| Gender              |       |       |       |       |
| Male                | 2090 | 17.87 | \( p < 0.0001 \) | 1747 | 20.31 | \( p = 0.0002 \) |
| Female              | 549  | 23.45 |          | 444  | 24.67 |          |
| Hepatic dysfunction (Baseline AST, ALT [U/L])\(^b\)|       |       |       |       |
| No (AST < 50 and ALT < 50) | 2065 | 19.32 | \( p = 0.8914 \) | 1740 | 21.24 | \( p = 0.9014 \) |
| Mild (AST 50 to <100 or ALT 50 to <100) | 222  | 18.67 |          | 175  | 21.70 |          |
| Moderate (AST 100 to <500 or ALT 100 to <500) | 45   | 17.97 |          | 30   | 19.74 |          |
| Severe (AST ≥500 or ALT ≥500) | 1    | 32.95 |          | 0    | –     |          |
| Unknown             | 306  | 17.42 |          | 246  | 20.70 |          |
| Renal dysfunction (baseline eGFR [mL/min/1.73 m²])\(^b\)|       |       |       |       |
| No (≥90)            | 149  | 19.46 | \( p = 0.1460 \) | 123  | 20.64 | \( p = 0.5141 \) |
| Mild (60 to <90)    | 871  | 19.59 |          | 730  | 21.00 |          |
| Moderate (30 to <60) | 1030 | 19.57 |          | 866  | 21.83 |          |
| Severe (15 to <30)  | 254  | 16.15 |          | 210  | 18.80 |          |
| End stage renal failure (<15) | 153  | 16.27 |          | 109  | 21.54 |          |
| Unknown             | 182  | 19.22 |          | 153  | 21.99 |          |

\( ALT \) alanine transaminase, \( AST \) aspartate transaminase, \( eGFR \) estimated glomerular filtration rate

\( ^b \) The subjects were those whose laboratory values were at the start of administration and at each time after administration

\( ^a \) Judgment based only on baseline clinical test values

5 Conclusions

As a result of the study under actual conditions of use, there were no new findings that would raise questions about the safety of topiroxostat, and the efficacy of this drug was shown to be the same as had been reported in clinical studies at the time of approval. Therefore, topiroxostat is considered to be a safe and effective drug for gout and hyperuricemia in daily practice.

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Ethics approval This study was carried out in accordance with the good post-marketing study practice standards specified by the Ministry of Health, Labor and Welfare in Japan. According to good post-marketing study practice in Japan, ethics approval was not required for this post-marketing study.

Informed consent According to good post-marketing study practice in Japan, informed consent was not required for this post-marketing study. As such, informed consent was not obtained from the individual participants included in the study.

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