

Reviewer's comments:

- *The incidence of combined SAEs in randomized controlled portions of the phase 3 studies appears higher in febuxostat group compared to allopurinol group*
- *The incidence of combined SAEs in long-term extension studies appears higher in allopurinol group compared to febuxostat allopurinol group.*
- *Interpretation of such inconsistency in results between randomized controlled trials and their extension phase is difficult. Combined category of SAE is a broad group of different events and does not provide the information about the incidence of individual groups of SAE, and CV SAE in particular. Further analysis is provided below.*

Table 5 (Sponsor's Table 3.4.b). Treatment-Emergent Serious Adverse Events by Patient-Years of Exposure (>0.1 Event Per 100 PY and >2 Events in at Least 1 Group) in Long-Term Extension Studies

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| MedDRA High Level Term MedDRA Preferred Term | Treatment Group | | | | |
|---|----------------------------------|---------------------------------|------------------------------------|------------------------------------|---|
| | Febuxostat | | | | Allopurinol 300/100 mg QD (N=178) (PY=133.3) |
| | Total (N=1143) (PY=1933.7) | 40 mg QD (N=12) (PY=33.0) | 80 mg QD (N=910) (PY=1265.4) | 120 mg QD (N=522) (PY=635.3) | |
| Number of Treatment-Emergent SAEs Per 100 PY | | | | | |
| Total Events | 9.5 | 21.2 | 9.9 | 8.0 | 11.3 |
| Coronary Artery Disorders NEC Coronary Artery Disease, Coronary Artery Occlusion, Coronary Artery Stenosis | 0.6 | 0 | 0.7 | 0.5 | 0.8 |
| Heart Failures NEC Cardiac Failure Congestive | 0.4 | 0 | 0.2 | 0.6 | 0.8 |
| Ischemic Coronary Artery Disorders Acute Myocardial Infarction, Angina Pectoris, Angina Unstable, Myocardial Infarction | 1.0 | 0 | 1.3 | 0.6 | 0.8 |
| Supraventricular Arrhythmias Atrial Fibrillation | 0.3 | 0 | 0.3 | 0.3 | 0.8 |
| Inner Ear Signs and Symptoms Vertigo | 0.2 | 0 | 0 | 0.5 | 0 |
| Duodenal and Small Intestinal Stenosis and Obstruction Small Intestinal Obstruction | 0.1 | 0 | 0.2 | 0 | 0 |
| Pain and Discomfort NEC Chest Pain, Non-Cardiac Pain | 0.2 | 0 | 0.2 | 0.2 | 0 |
| Cholecystitis and Cholelithiasis Cholecystitis, Cholecystitis Acute, Cholelithiasis | 0.4 | 3.0 | 0.6 | 0 | 0 |
| Abdominal and Gastrointestinal Infections Appendicitis, Diverticulitis | 0.3 | 0 | 0.2 | 0.5 | 1.5 |
| Bacterial Infections NEC Cellulitis | 0.2 | 0 | 0.2 | 0.2 | 0 |
| Lower Respiratory Tract and Lung Infections Bronchiectasis, Lobar Pneumonia, Pneumonia | 0.6 | 6.1 | 0.5 | 0.5 | 0 |
| Sepsis, Bacteraemia and Viraeamia Sepsis, Urosepsis | 0.2 | 0 | 0.2 | 0 | 0 |
| Non-Site Specific Injuries NEC Excoriation, Fall | 0.1 | 0 | 0.2 | 0 | 0 |

SAE = serious adverse event; PY = patient-years of exposure; NEC = not elsewhere classified

Studies included: TMX-01-005 and C02-021

Cross-reference: Statistical Table 3.1.10

| MedDRA High Level Term MedDRA Preferred Term | Treatment Group | | | | |
|---|----------------------------------|---------------------------------|------------------------------------|------------------------------------|---|
| | Febuxostat | | | | Allopurinol 300/100 mg QD (N=178) (PY=133.3) |
| | Total (N=1143) (PY=1933.7) | 40 mg QD (N=12) (PY=33.0) | 80 mg QD (N=910) (PY=1265.4) | 120 mg QD (N=523) (PY=635.3) | |
| Non-Site Specific Procedural Complications Incisional Hernia, Post Procedural Complication, Procedural Complication | 0.2 | 0 | 0.2 | 0 | 0 |
| Intervertebral Disc Disorders NEC Intervertebral Disc Degeneration, Intervertebral Disc Disorder, Intervertebral Disc Protrusion | 0.2 | 0 | 0 | 0.5 | 0.8 |
| Joint Related Disorders NEC Rotator Cuff Syndrome | 0.1 | 0 | 0.2 | 0 | 0 |
| Osteoarthropathies Osteoarthritis | 0.5 | 0 | 0.3 | 0.8 | 0 |
| Spine and Neck Deformities Cervical Spinal Stenosis, Lumbar Spinal Stenosis, Spinal Column Stenosis | <0.1 | 3.0 | 0 | 0 | 1.5 |
| Central Nervous System Haemorrhages and Cerebrovascular Accidents Brain Stem Infarction, Cerebral Haemorrhage, Cerebrovascular Accident | 0.4 | 3.0 | 0.4 | 0.3 | 0 |
| Central Nervous System Vascular Disorders NEC Carotid Artery Stenosis, Lacunar Infarction | 0.2 | 0 | 0.2 | 0.2 | 0 |
| Disturbances in Consciousness NEC Syncope | 0.1 | 0 | 0.2 | 0 | 0 |
| Renal Failure and Impairment Renal Failure, Renal Failure Acute | 0.1 | 0 | 0.2 | 0 | 0 |
| Bronchospasm and Obstruction Asthma, Chronic Obstructive Airways Disease Exacerbated | 0.1 | 0 | 0.2 | 0 | 0 |
| Pulmonary Thrombotic and Embolic Conditions Pulmonary Embolism | 0.2 | 0 | 0.2 | 0 | 0.8 |
| Peripheral Aneurysms and Dissections Femoral Artery Aneurysm, Peripheral Artery Aneurysm | 0.1 | 0 | 0 | 0.3 | 0 |

SAE = serious adverse event; PY = patient-years of exposure; NEC = not elsewhere classified
Studies included: TMX-01-005 and C02-021
Cross-reference: Statistical Table 3.1.10

Subjects who had SAEs that occurred since the 4-Month Safety Update and previously reported subjects for whom new clinically significant information became available are summarized in **Table 3.4.d. (see Appendix 1).**

Reviewer's comments:

In the long-term extension studies:

- *The incidence of individual SAEs is comparable between febuxostat and allopurinol treatment groups.*
- *The incidence of SAE of interest-MedDRA High Level Term of Ischemic Coronary Artery Disorder- is slightly higher in febuxostat group (1.0) compared to allopurinol group (0.8). More detailed analysis of this portion of data is provided below under Cardiovascular SAE*
- *No dose response was observed for febuxostat*
- *There was no obvious change in the pattern of specific adverse events*
- *The data update came from ongoing open-label studies which makes these data less reliable and harder to interpret*

7.1.2.1 Cardiovascular SAEs

To address the concern of the FDA regarding the potential risk of cardiovascular/thrombotic adverse events, the Sponsor performed several new analyses within the cardiovascular organ system. This submission includes analyses based on the widely used endpoint of the Antiplatelet Trialists' Collaboration study (APTC) (nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death). This post hoc analysis was performed by a cardiologist Dr. White who adjudicated cardiovascular adverse events. The adjudicator was blinded to treatment group and type of study. Primary APTC events were defined as follows: cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and non-fatal cardiac arrest. Secondary APTC events included angina, coronary revascularization, transient ischemic attack (TIA), venous or arterial vascular thrombotic events, and congestive heart failure. Of note, non-fatal cardiac arrest and non-fatal congestive heart failure (CHF) were not part of the APTC terms described in the literature, but were added by the Sponsor and are included in the APTC event analyses in this document as suggested by Dr White.

APTC events were analyzed based on investigator-reported events. For this analysis, MedDRA preferred terms for all adverse events in the Sponsor's database that corresponded to the primary and secondary APTC events were identified by the Sponsor.

Table 6 (Sponsor's Table 3.6.b). APTC Criteria and Corresponding MedDRA Preferred Terms in the TAP Database for the Investigator-Reported Analyses

| APTC Criterion | MedDRA Preferred Term | Category |
|---|--|---|
| Cardiovascular death | The following MedDRA PTs were associated with cardiovascular death: Acute myocardial infarction Cardiac arrest Cardiac failure congestive Myocardial infarction Retroperitoneal haemorrhage | These events are summarized as primary APTC events in this document |
| Non-fatal myocardial infarction | Acute myocardial infarction ^a Myocardial infarction ^a Silent myocardial infarction ^a | |
| Non-fatal stroke | Brain stem infarction ^a Cerebrovascular accident ^a Lacunar infarction ^a Cerebral haemorrhage ^a | |
| Non-fatal cardiac arrest | Cardiac arrest ^a | |
| Angina | Acute coronary syndrome Angina pectoris Angina unstable | These events are summarized as secondary APTC events in this document |
| Revascularization | Coronary artery atherosclerosis ^b Coronary artery disease ^b Coronary artery occlusion ^b Coronary artery stenosis ^b | |
| Transient ischemic attack | Transient ischaemic attack | |
| Venous and peripheral arterial vascular thrombotic events | Pulmonary embolism Deep vein thrombosis Thrombosis Ischaemia | |
| Non-fatal congestive heart failure | Cardiac failure congestive ^b | |

a Only non-fatal events

b Approximately 85% of the reported events also had documentation of revascularization

Cross-reference: Statistical Table 3.14

Reviewer's comments:

- *The following adverse events combined into a group of secondary APTC events are thrombotic in nature: angina, TIA, venous and arterial thrombotic events. The coronary revascularization is a procedure, not necessarily an adverse event, and is performed in patients with underlying coronary artery disease. This reviewer disagrees with inclusion of this procedure in a group of thrombotic events.*

- *This reviewer disagrees with inclusion of CHF into the group of thrombotic events (secondary APTC) since CHF is not necessarily viewed as thrombotic in nature and could be a result of a previous thrombotic event such as myocardial infarction.*
- *Since both coronary revascularization and CHF are quite common events in the general population and in a gout population in particular, including them in a group of thrombotic events might dilute the results and therefore obscure the possible risk of true thrombotic events.*

The adjudicator's review of the clinical data resulted in a listing of 113 events (Table 7).

Table 7. Event Summary by category

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| 1. APTC events N = 34 | 2. non-APTC Cardiovascular thrombotic N = 36 | 3. CHF or valvular disease N = 6 | 4. Arrhythmia, non-ischemic N = 12 | 5. Non-CV event N = 25 | |
|---------------------------------|--|--|--|----------------------------------|--|
| 310 | 2002 | 2131 | 1021 | 1042 | |
| 4516 | 2119 | 2865 | 1092 | 2024 | |
| K007-22 | 2158 | 4175 | 1100 | 2315 | |
| 28-054 | 2316 | 4633 | 1122 | 2376 | |
| 1152 | 2578 | 4753 | 2610 | 2609 | |
| 2004 | 2606 | 5000 | 2817 | 2658 | |
| 2019 | 2685 | | 4308 | 2789 | |
| 2055 | 4821 | | 4458 | 4092 | |
| 2270 | N/A (DCS) | | 4478 | 4095 | |
| 2334 | 2499 | | 4632 | 4172 | |
| 2403 | 2062 | | 4744 | 4240 | |
| 2433 | 2063 | | 4830 | 4518 | |
| 2487 | 2068 | | | 4551 | |
| 2565 | 2223 | | | 4639 | |
| 2695 | 2244 | | | 4764 | |
| 2779 | 2382 | | | 2199 | |
| 2823 | 2559 | | | 2201 | |
| 4064 | 2673 | | | 2356 | |
| 4186 | 2686 | | | 2480 | |
| 4245 | 2790 | | | 2584 | |
| 4263 | 4029 | | | 2761 | |
| 4303 | 4056 | | | 4087 | |
| 4329 | 4302 | | | 4313 | |
| 4409 | 4371 | | | 4641 | |
| 4470 | 4508 | | | 2377 | |
| 4479 | 4670 | | | | |
| 4756 | 4674 | | | | |
| 4811 | 4730 | | | | |
| 4893 | 4775 | | | | |
| 4916 | 4776 | | | | |
| 4959 | 4813 | | | | |
| 6007 | 4887 | | | | |
| 6017 | 4907 | | | | |
| 83690 | 4950 | | | | |
| | 4963 | | | | |
| | 4112 | | | | |

The majority of cases adjudicated by Dr. White, required no reclassification (cases did not require change in classification, n=77). There were 6 events re-classified from non-APTC to APTC events (subjects ID 310, 2019, 2403, 2487, 4186, and 4959) and there were 5 events re-classified from APTC to non-APTC events (subjects ID 2223, 2790, 4730, 4963, and 5000). Additionally, there were 25 events re-classified from cardiovascular or potentially cardiovascular to a non-cardiovascular diagnosis.

Reviewer's comments:

- It appears, that the following subjects included in **Table 7** were submitted with the original NDA: 4186, 2865, 2610, 4308, 4172, 2686, 2199, 2004, 4775, 2024, 1152
- A total of 65 subjects had **new treatment-emergent CV SAEs** since the 4-Month Safety Update: 4 in allopurinol group and 61 in febuxostat groups.
- According to Dr. White's adjudication, **14 out of 61 in the febuxostat group** were adjudicated as **APTC events** (subjects 2609, 4959, 4756, 4329, 2823, 6017, 4916, 4893, 4409, 4303, 4245, 4112, 4064, 2055) and **11 events** were adjudicated as **non-APTC-cardiovascular** (subjects 4776, 4887, 4302, 2578, 4821, 4730, 2790, 2673, 2316, 2119, 2062)
- **In allopurinol group, 1 out of 4 events was an APTC event** (subject 4811)

The cardiovascular adverse events are summarized both by percentage of subjects with an event without adjustment for exposure, and by adjusting for patient-years of exposure for all study groupings. For the Phase 3 and Phase 2/3 randomized controlled studies groupings, the primary focus is on the analyses of the percentage of subjects with an event. For the long-term extension studies grouping, the primary focus is on the exposure-adjusted analysis due to substantial differences in duration of exposure among treatment groups. The much smaller number of patient-years of exposure on allopurinol compared to febuxostat in the long-term extension studies limited the value of observed incidence rates for infrequent events such as APTC events.

The percentages of subjects with investigator-reported, treatment-emergent primary APTC events in the Phase 3 randomized controlled studies are presented in **Table 8**.

Table 8 (Modified Sponsor’s Table 3.6.e). Incidence Rates and Confidence Intervals for Subjects with Investigator-Reported Treatment-Emergent Primary APTC Events in the Phase 3 Randomized Controlled Studies

| Primary APTC Events | Treatment Group, n (%) | | | | | |
|---------------------------------|------------------------|--------------------------|-------------------------|-------------------------|----------------------|---|
| | Placebo (N=134) | Febuxostat | | | | Allopurinol 300/100 mg QD (N=521) |
| | | Total (N=1177) | 80 mg QD (N=523) | 120 mg QD (N=520) | 240 mg QD (N=134) | |
| Overall | 0 (0.00-2.71) | 9 (0.8) (0.35-1.45) | 4 (0.8) (0.21-1.95) | 5 (1.0) (0.31-2.23) | 0 (0.00-2.71) | 1 (0.2) (0.005-1.07) |
| CV death | 0 (0.00-2.71) | 3 (0.3) (0.053-0.74) | 2 (0.4) (0.046-1.37) | 1 (0.2) (0.005-1.07) | 0 (0.00-2.71) | 0 (0.00-0.706) |
| Non-fatal myocardial infarction | 0 (0.00-2.71) | 5 (0.4) (0.14-0.99) | 2 (0.4) (0.046-1.37) | 3 (0.6) (0.119-1.68) | 0 (0.00-2.71) | 1 (0.2) (0.005-1.065) |
| Non-fatal stroke | 0 (0.00-2.71) | 1 (0.08) (0.002-0.47) | 0 (0.00-0.70) | 1 (0.2) (0.005-1.07) | 0 (0.00-2.71) | 0 (0.00-0.706) |
| Non-fatal cardiac arrest | 0 (0.00-2.71) | 1 (0.08) (0.002-0.47) | 0 (0.00-0.70) | 1 (0.2) (0.005-1.07) | 0 (0.00-2.71) | 0 (0.00-0.706) |

Studies included: C02-009 and C02-010

Adverse events summarized were reported after the first dose of study drug and within 30 days of the last dose of study drug, a CI calculated based on binomial distribution.

Cross-reference: Statistical Table 3.17.2.1

Reviewer’s comments:

- *The Sponsor appears to miscalculate the total number of events. The correct total number of events in the febuxostat group including deaths is 10 (0.85) (6 events in 120-mg febuxostat group instead of 5 as calculated by the Sponsor). This is more than four times higher in febuxostat group compared to allopurinol or placebo group*
- *There are seven (5+1+1=7) non-fatal primary APTC events (non-fatal MI, stroke and cardiac arrest) with the incidence rate of 0.6 and that is still three times higher compared to the incidence of such events in allopurinol (0.2) or placebo group(0)*
- *The numbers appear to be small, however APTC events are considered to be rare events, and the difference between two groups is very concerning suggesting that febuxostat poses an increased risk of cardio-vascular adverse events*

The percentages of subjects with treatment-emergent adjudicated APTC events in the Phase 3 randomized controlled studies are presented in Table 9.

Table 9 (Sponsor's Table 3.6.n). Percentages of Subjects with Treatment-Emergent Adjudicated APTC Events in the Phase 3 Randomized Controlled Studies

| | Treatment Group | | | | | |
|---------------------|--------------------|-------------------|---------------------|----------------------|---|----------------------|
| | Placebo (N=134) | Febuxostat | | | Allopurinol 300/100 mg QD (N=531) | |
| | | Total (N=1177) | 80 mg QD (N=523) | 120 mg QD (N=520) | | 240 mg QD (N=134) |
| APTC Events | | | | | | |
| Number of Subjects | 0 | 7 | 4 | 3 | 0 | 1 |
| Rate (%) | 0 | 0.59 | 0.76 | 0.58 | 0 | 0.19 |
| 95% CI ^a | (0.00-2.71) | (0.239-1.22) | (0.209-1.95) | (0.119-1.68) | (0.00-2.71) | (0.005-1.07) |
| CV Death | | | | | | |
| Number of Subjects | 0 | 3 | 2 | 1 | 0 | 0 |
| Rate (%) | 0 | 0.25 | 0.38 | 0.19 | 0 | 0 |
| 95% CI ^a | (0.00-2.71) | (0.053-0.743) | (0.046-1.37) | (0.005-1.07) | (0.00-2.71) | (0.00-0.706) |
| Non-fatal MI | | | | | | |
| Number of Subjects | 0 | 4 | 2 | 2 | 0 | 1 |
| Rate (%) | 0 | 0.34 | 0.38 | 0.38 | 0 | 0.19 |
| 95% CI ^a | (0.00-2.71) | (0.093-0.868) | (0.046-1.37) | (0.047-1.38) | (0.00-2.71) | (0.005-1.07) |

Studies included: C02-009 and C02-010

^a The confidence intervals are calculated based on binomial distribution

Cross-reference: Statistical Table 3.19.2.1

Reviewer's comments:

- *Compared to non-adjudicated events (Table 8), three events in febuxostat group were adjudicated by the Sponsor as non-APTC: one non-fatal stroke, one non-fatal myocardial infarction and one non-fatal cardiac arrest. Those events were retained in a category of APTC events in a consult by the cardio-renal Division (Appendix 2)*
- *The overall and individual events incidence rate of Sponsor-adjudicated primary APTC events is only slightly lower than that of non-adjudicated events (Table 8), and when compared to allopurinol group, it is two times higher for non-fatal MI (0.34 vs. 0.19) and three times higher for combined fatal +non-fatal APTC events (0.59 vs. 0.19).*

The percentages of subjects with investigator-reported treatment-emergent primary AND secondary APTC events in the Phase 3 randomized controlled studies are presented in **Table 10.**

Table 10. (Modified Sponsor's Table 3.6.f). Incidence Rates and Confidence Intervals for Subjects with Treatment-Emergent Primary and Secondary Investigator-Reported APTC Events in the Phase 3 Randomized Controlled Studies

| Primary and Secondary APTC Events | Treatment Group, n (%) | | | | | |
|---|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|---|
| | Placebo (N=134) | Febuxostat | | | | Allopurinol 300/100 mg QD (N=521) |
| | | Total (N=1177) | 80 mg QD (N=523) | 120 mg QD (N=520) | 240 mg QD (N=134) | |
| Overall 95% CI ^a | 1 (0.7) (0.019-4.09) | 25 (2.1) (1.38-3.12) | 13 (2.5) (1.33-4.31) | 11 (2.1) (1.05-3.75) | 1 (0.7) (0.019-4.09) | 7 (1.3) (0.54-2.75) |
| CV death | 0 | 3 (0.3) | 2 (0.4) | 1 (0.2) | 0 | 0 |
| Non-fatal myocardial infarction | 0 | 5 (0.4) | 2 (0.4) | 3 (0.6) | 0 | 1 (0.2) |
| Non-fatal stroke | 0 | 1 (<0.1) | 0 | 1 (0.2) | 0 | 0 |
| Non-fatal cardiac arrest | 0 | 1 (<0.1) | 0 | 1 (0.2) | 0 | 0 |
| Angina | 0 | 6 (0.5) | 4 (0.8) | 1 (0.2) | 1 (0.7) | 2 (0.4) |
| Revascularization | 1 (0.7) | 6 (0.5) | 4 (0.8) | 2 (0.4) | 0 | 4 (0.8) |
| Transient Ischemic Attack | 0 | 2 (0.2) | 2 (0.4) | 0 | 0 | 0 |
| Venous and peripheral arterial vascular thrombotic events | 0 | 2 (0.2) | 0 | 2 (0.4) | 0 | 0 |
| Non-fatal congestive heart failure | 0 | 3 (0.3) | 2 (0.4) | 1 (0.2) | 0 | 1 (0.2) |

Studies included: C02-009 and C02-010

^a CI calculated based on binomial distribution

Cross-reference: Statistical Table 3.16.4.1 and 3.17.2.3

Reviewer's comments:

- *The overall incidence and the incidence of individual investigator-reported APTC and other thrombotic events (other than revascularization) are consistently higher in febuxostat group compared to allopurinol and placebo groups in phase 3 controlled studies.*

- *The Sponsor appears to miscalculate the total number of events in this table. The correct total number of events in febuxostat group is 29 (2.46) and is two times higher compared to allopurinol group (8 events or a rate of 1.3)*
- *Since revascularization and CHF are not thrombotic events, after excluding those events from a calculation, it appears that the overall rate of thrombotic events in febuxostat group is 1.7 (20 events) vs 0.5 (3 events) in allopurinol group that is more than **3 time higher** in febuxostat compared to allopurinol*

The overall incidence of investigator-reported, primary APTC events per 100 patient-years of exposure in the long-term extension studies are presented in **Table 11**.

Table 11 (Updated Sponsor’s Table 3.6.g). Incidence of Investigator-Reported Treatment-Emergent Primary APTC Events per 100 Patient-Years of Exposure in the Long-Term Extension Studies

| Primary APTC Events | Treatment group | | | | |
|---|---------------------------------|-----------------------------|--------------------------------|---------------------------------|--|
| | Total N=1143 PY=1933.7 | Febuxostat | | | Allopurinol 300/100 mg QD N=178 PY=133.3 |
| | | 40 mg QD N=12 PY=33.0 | 80 mg QD N=910 PY=1265.4 | 120 mg QD N=522 PY=635.3 | |
| Overall 95% CI | 29 (1.50) (0.96-2.09) | 1 (3.0) (0.077-16.89) | 18 (1.4) (0.84-2.25) | 10 (1.57) (0.65-2.69) | 1 (0.75) (0.019-4.18) |
| CV death 95% CI | 5 (0.26) | 0 (0-11.2) | 1 (<0.1) (0.002-0.44) | 4 (0.63) | 0 (0-2.77) |
| Non-fatal myocardial infarction 95% CI | 15 (0.8) (0.43-1.28) | 0 (0-11.2) | 12 (0.9) (0.490-1.66) | 3 (0.5) (0.097-1.38) | 1 (0.8) (0.19-4.18) |
| Non-fatal stroke 95% CI | 9 (0.5) (0.21-0.884) | 1 (3.0) (0.077-16.9) | 5 (0.4) (0.128-0.922) | 3 (0.5) (0.097-1.38) | 0 (0-2.77) |

N=number of subjects dosed; PY-patient year
Studies included: C02-021 and TMX-01-005
Cross-reference: Statistical Table 3.16.1.2 and 3.17.1.2

Reviewer’s comments:

- *Table was amended by this reviewer: one death was added to the Table in febuxostat 120 mg group and the total number of events/incidence were recalculated (in bolds)*
- *The overall incidence of primary APTC events in long-term open-label extension studies is two times higher in febuxostat group (1.50) compared to allopurinol group (0.75), when adjusted for the differences in exposure between treatment groups.*
- *The Sponsor did not include additional two deaths in febuxostat group, therefore the rates are miscalculated*

The incidence of treatment-emergent **adjudicated** APTC events per 100 patient-years in the long-term extension studies are presented in Table 12.

Table 12 (Sponsor's Table 3.6.r) Incidence of Treatment-Emergent Adjudicated APTC Events Per 100 Patient-Years of Exposure in the Long-Term Extension Studies

| | Treatment Group | | | | |
|-------------------------|----------------------------------|---------------------------------|------------------------------------|------------------------------------|---|
| | Febuxostat | | | | Allopurinol 300/100 mg QD (N=178) (PY=133.3) |
| | Total (N=1143) (PY=1933.7) | 40 mg QD (N=12) (PY=33.0) | 80 mg QD (N=910) (PY=1265.4) | 120 mg QD (N=522) (PY=635.3) | |
| APTC Events | | | | | |
| Number of Subjects | 21 | 1 | 12 | 8 | 1 |
| Rate per 100 PY | 1.09 | 3.03 | 0.95 | 1.26 | 0.75 |
| 95% CI ^a | (0.672-1.66) | (0.077-16.9) | (0.490-1.65) | (0.544-2.48) | (0.019-4.18) |
| CV Death | | | | | |
| Number of Subjects | 4 | 0 | 1 | 3 | 0 |
| Rate per 100 PY | 0.21 | 0 | 0.08 | 0.47 | 0 |
| 95% CI ^a | (0.056-0.530) | (0-11.2) | (0.002-0.440) | (0.097-1.38) | (0-2.77) |
| Non-fatal MI | | | | | |
| Number of Subjects | 9 | 0 | 7 | 2 | 1 |
| Rate per 100 PY | 0.47 | 0 | 0.55 | 0.31 | 0.75 |
| 95% CI ^a | (0.213-0.884) | (0-11.2) | (0.222-1.14) | (0.038-1.14) | (0.019-4.18) |
| Non-fatal Stroke | | | | | |
| Number of Subjects | 8 | 1 | 4 | 3 | 0 |
| Rate per 100 PY | 0.41 | 3.03 | 0.32 | 0.47 | 0 |
| 95% CI ^a | (0.179-0.815) | (0.077-16.9) | (0.086-0.809) | (0.097-1.38) | (0-2.77) |

Studies included: TMX-01-005 and C02-021

a The confidence intervals are calculated based on Poisson distribution

Cross-reference: Statistical Table 3.19.1.2

Reviewer's comments:

- Overall rate of primary adjudicated APTC events in long-term extension studies is higher in Febuxostat group compared to allopurinol group.
- 2 additional deaths in febuxostat group are not included in the calculation. As mentioned earlier in this review, these data came from ongoing open-label trials. Since febuxostat exposure is greater than allopurinol exposure during the open-label portion of the trials, it makes these data difficult to interpret. However, it seems that a trend toward increased cardiovascular adverse events in the febuxostat group compared to allopurinol remains after differences in exposure are taken into account

Reviewer's comments on cardiovascular adverse events analyses:

- Review of the Sponsor's **adjudicated** cardiovascular adverse events that occurred during phase 3 controlled studies does not change the conclusion reached by this reviewer in original NDA review. The rate of APTC cardiovascular adverse events, both non-adjudicated and adjudicated, is three to four times higher in patients exposed to febuxostat compared to those exposed to allopurinol.
- The incidence rates of different individual non-adjudicated primary APTC events in phase 3 controlled studies is three to four times higher in febuxostat group compared to allopurinol group
- The incidence rates of different individual adjudicated primary APTC events in phase 3 controlled studies is two to three times higher in febuxostat group compared to allopurinol group
- The incidence rates of different individual non-adjudicated primary and secondary APTC events (more inclusive) in phase 3 controlled studies is three times higher in febuxostat group compared to allopurinol group
- The incidence rates of different individual non-adjudicated primary APTC events in long-term extension studies is two times higher in febuxostat group compared to allopurinol group when adjusted for the difference in exposure

- *The incidence rates of different individual adjudicated primary APTC events in long-term extension studies is 1.5 to two times higher in febuxostat group compared to allopurinol group when adjusted for the difference in exposure*
- *Since randomized controlled trials are viewed as the gold standard for evaluating efficacy and safety, the reanalysis of these trials database provides the most reliable information. These results are supported by similar trends observed in the open-label extension portions of the trials.*
- *These re-analyses confirmed the unfavorable risk/benefit profile of febuxostat in regard to cardiovascular adverse events compared to allopurinol in a population that had no apparent differences in baseline characteristics.*

Additional data from Japan development program

In brief, the Japanese development program examined doses of febuxostat that are not intended for an approval under this application (up to 40 mg). During the Phase 2 and Phase 3 studies, approximately 400 subjects received febuxostat for up to 8 weeks. Approximately 340 additional subjects received febuxostat for up to either 28 or 52 weeks. There were no new SAEs reported since the 4-Month Safety Update for the Japanese clinical studies.

Overall, 2 cardiovascular SAEs have been reported in the Japanese studies. A previously reported serious cardiovascular event included a Putamen Haemorrhage (Subject 28-054; Study TMX-67-11; febuxostat 10 mg to 20 mg QD; Appendix 13.3.4 of the original ISS). In addition, a subject who was assigned to febuxostat (Study TMX-67-11; Subject K007-22; febuxostat 10 mg) developed an aortic aneurysm rupture and subsequently died; however, available data indicated that no study drug was taken.

7.1.3.2 Adverse events associated with dropouts

Since the 4-Month Safety Update, 19 subjects prematurely discontinued the long-term extension studies due to adverse events. Below is the list of subjects who discontinued from the study since the 4-month Safety Update.

Clinical Review
Tatiana Oussova, MD, MPH
NDA 21-856/S-01
Uloric/Febuxostat tablets 80 mg and 120 mg

Table 13 (Sponsor's Table 3.5.d). Subjects Who Prematurely Discontinued Study Drug Due to Adverse Events in the Long-Term Extension Studies since the 4-Month Safety Update

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Clinical Review
 Tatiana Oussova, MD, MPH
 NDA 21-856/S-01
 Uloric/Februxostat tablets 80 mg and 120 mg

| Study No./Phase | Subject/Age/Gender | Adverse Event (MedDRA Preferred Term) | Relationship to Study Drug | Severity | Day of Onset ^a | Duration (Days) ^b | SAE | Alternative Etiology |
|-----------------------------|--------------------|---------------------------------------|----------------------------|----------|---------------------------|------------------------------|-----|-----------------------------------|
| Febuxostat 80 mg QD | | | | | | | | |
| C02-021/3 | 2074/55/Male | Malignant Melanoma | Possible | Mild | 536 [900] | 2 days | No | Atypical nevi |
| C02-021/3 | 4028/63/Male | Liver Function Test Abnormal | Possible | Moderate | 31 [241] | Ong (211) | No | Possible fatty liver |
| C02-021/3 | 4143/45/Male | Alanine Aminotransferase Increased | Possible | Moderate | 366 [567] | Ong (512) | No | Diet |
| | | Aspartate Aminotransferase Increased | Possible | Moderate | 366 [567] | Ong (512) | No | Diet |
| C02-021/3 | 4747/61/Male | Urticaria | Possible | Moderate | 277 [476] | 12 hours | No | Possible infection versus allergy |
| | | Urticaria | Possible | Moderate | 284 [483] | 12 hours | No | |
| | | Urticaria | Possible | Moderate | 291 [490] | 12 hours | No | |
| Febuxostat 120 mg QD | | | | | | | | |
| C02-021/3 | 2183/56/Male | Hepatic Enzyme Increased | Possible | Mild | 306 [670] | Ong (439) | No | Underlying liver disease |

SAE = serious adverse event; Ong = ongoing

Note: For subjects in Study TMX-01-005, age is at time of entry in Study TMX-00-004. For subjects in Study C02-021, age is at time of entry in Study C02-009 or C02-010.

Note: Subjects are categorized by treatment received during the most recent adverse event that occurred during the long-term extension study.

a Numbers in brackets represent cumulative study days since first dose of study drug.

b AE was ongoing as of study day in parentheses; duration in days unless otherwise specified.

Cross-references: Statistical Tables 7.2.1 and 7.3 and TAP Pharmacovigilance database

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| Study No./Phase | Subject/Age/Gender | Adverse Event (MedDRA Preferred Term) | Relationship to Study Drug | Severity | Day of Onset ^a | Duration (Days) ^b | SAE | Alternative Etiology |
|------------------------------|--------------------|---------------------------------------|----------------------------|----------|---------------------------|------------------------------|-----|--|
| Febuxostat 80 mg QD | | | | | | | | |
| C02-021/3 | 2035/70/Female | Cerebrovascular Accident | Unlikely | Severe | 465 [833] | 50 | Yes | Hypertension |
| C02-021/3 | 2082/72/Male | Deep Vein Thrombosis | Unlikely | Moderate | 676 [1042] | 4 | No | Atherosclerosis |
| | | Pulmonary Embolism | Unlikely | Severe | 676 [1042] | 4 | Yes | Atherosclerosis with thrombosis |
| C02-021/3 | 3528/40/Male | Blood Triglycerides Increased | Not Related | Severe | 1 [365] | Ong (453) | No | Diet |
| C02-021/3 | 4066/44/Male | Cholecystitis Acute | Not Related | Severe | 553 [749] | 14 | Yes | Cholecystitis |
| | | Procedural Complication | Not Related | Moderate | 557 [753] | 9 | Yes | Surgical bile clipping |
| C02-021/3 | 4097/70/Female | Breast Cancer Recurrent | Not Related | Severe | 665 [891] | Ong (666) | Yes | Recurrence of breast cancer |
| C02-021/3 | 4305/63/Male | Acute Myocardial Infarction | Not Related | Severe | 521 [715] | 9 | Yes | Hypertension |
| C02-021/3 | 4343/57/Male | Colon Cancer Metastatic | Unlikely | Severe | 409 [620] | 46 | Yes | Colon cancer is independent of drug therapy for govt |
| | | Colonic Polyp Diverticulum | Not Related | Moderate | 415 [626] | unknown | No | Hereditary |
| C02-021/3 | 4529/43/Male | Osteoarthritis | Not Related | Moderate | 415 [626] | 40 | No | Acquired bowel disease |
| C02-021/3 | 4959/71/Male | Osteoarthritis | Not Related | Severe | 554 [749] | Ong (639) | Yes | Osteoarthritis |
| | | Cardiac Failure Congestive | Not Related | Severe | 367 | 4 | Yes | Underlying disease progression for Cardiac Failure Congestive and Cardio-respiratory arrest. Cardiac arrest for Respiratory failure. |
| C02-021/3 | | Cardio-respiratory Arrest | Not Related | Severe | 370 | <1 | Yes | Underlying disease progression for Cardiac Failure Congestive and Cardio-respiratory arrest. Cardiac arrest for Respiratory failure. |
| | | Respiratory Failure | Not Related | Severe | 370 | <1 | Yes | Underlying disease progression for Cardiac Failure Congestive and Cardio-respiratory arrest. Cardiac arrest for Respiratory failure. |
| Febuxostat 120 mg QD | | | | | | | | |
| C02-021/3 | 2519/62/Female | Pulmonary Mass | Unlikely | Moderate | 59 [430] | 490 | No | Possible scar tissue or primary lung cancer |
| | | Non-Small Cell Lung Cancer | Not Related | Unknown | 549 [920] | 1 | Yes | Primary lung cancer |
| C02-021/3 | 2823/50/Male | Cerebral Haemorrhage | Not Related | Severe | 378 [744] | 26 | Yes | Hypertension |
| C02-021/3 | 4186/84/Female | Retroperitoneal Haemorrhage | Not Related | Severe | 432 [638] | 1 hour | Yes | Subject on Coumadin |
| C02-021/3 | 4351/72/Male | Oesophageal Carcinoma | Not Related | Moderate | 500 [697] | 64 | Yes | Chronic GERD |
| Allopurinol 300 mg QD | | | | | | | | |
| C02-021/3 | 4768/40/Male | Alanine Aminotransferase Increased | Unlikely | Mild | 365 [561] | Ong (428) | No | Diet |
| | | Aspartate Aminotransferase Increased | Unlikely | Mild | 365 [561] | Ong (428) | No | Diet |

SAE = serious adverse event; Ong = ongoing; GERD = gastroesophageal reflux disease

Note: For subjects in Study TMX-01-005, age is at time of entry in Study TMX-00-004. For subjects in Study C02-021, age is at time of entry in Study C02-009 or C02-010.

Note: Subjects are categorized by treatment received during the most recent adverse event that occurred during the long-term extension study.

a Numbers in brackets represent cumulative study days since first dose of study drug.

b AE was ongoing as of study day in parentheses; duration in days unless otherwise specified.

c Subject's reason for premature discontinuation is captured in the clinical database as "Other-Death," rather than as adverse event. Because the information in the clinical database indicates that it is unknown whether the subject took study drug after Day 322, the database shows that the fatal event occurred 58 days after the last dose of study drug. Information in the Pharmacovigilance database, however, suggests that the subject may have been taking study drug until the time of his death. Because of the discrepancy, it is unclear whether these fatal SAEs or previous AEs led to premature discontinuation; only the fatal SAEs are listed here.

Cross-references: Statistical Tables 7.2.1 and 7.3 and TAP Pharmacovigilance database

Treatment-emergent and treatment-related adverse events that led to premature discontinuation by PY for the long-term extension studies and for the Phase 3 randomized controlled studies, are summarized in **Table 14**.

Table 14 (Sponsor’s Table 3.5.a). Incidence of Adverse Events that Led to Discontinuation by Patient-Years of Exposure in Long-Term Extension Studies and Phase 3 Randomized Controlled Studies

| Number of Adverse Events that Led to Premature Discontinuation Per 100 PY | | | | | | | |
|--|---------------------------|----------------------------|---------------------------|------------------------------|------------------------------|-----------------------------|--|
| Long-Term Extension Studies | – | Febuxostat | | | | | Allopurinol 300/100 mg QD (N=178) (PY=133.3) |
| | | Total (N=1143) (PY=1933.7) | 40 mg QD (N=13) (PY=33.0) | 80 mg QD (N=910) (PY=1265.4) | 120 mg QD (N=522) (PY=635.3) | – | |
| Phase 3 Randomized Controlled Studies | Placebo (N=134) (PY=59.9) | Total (N=1177) (PY=671.1) | – | 80 mg QD (N=523) (PY=312.6) | 120 mg QD (N=520) (PY=304.5) | 240 mg QD (N=134) (PY=54.0) | Allopurinol 300/100 mg QD (N=521) (PY=333.7) |
| Treatment-Emergent Adverse Events that Led to Premature Discontinuation Per 100 PY | | | | | | | |
| Long-Term | -- | 4.4 | 6.1 | 5.0 | 3.1 | -- | 3.0 |
| Phase 3 | 15.0 | 20.7 | -- | 18.2 | 18.4 | 48.1 | 12.3 |
| Treatment-Related Adverse Events that Led to Premature Discontinuation Per 100 PY | | | | | | | |
| Long-Term | -- | 2.4 | 6.1 | 2.4 | 2.0 | -- | 0.8 |
| Phase 3 | 10.0 | 11.5 | -- | 8.6 | 10.8 | 31.5 | 7.5 |

PY = patient-years of exposure

Long-term extension studies included: TMX-01-005 and C02-021

Phase 3 randomized controlled studies included: C02-009 and C02-010

Cross-references: Statistical Tables 3.1.8, 3.1.9, 3.2.8, and 3.2.9

Compared to the Phase 3 randomized controlled studies, the overall incidence of treatment-emergent adverse events by PY that led to discontinuation in the long-term extension studies was lower in every treatment group. Per 100 PY in the febuxostat total group, 4.4 events in the long-term extension studies and 20.7 events in the Phase 3 randomized controlled studies led to premature discontinuation.

In the allopurinol 300/100-mg QD group in the long-term extension studies and Phase 3 randomized controlled studies, 3.0 and 12.3 adverse events per 100 PY, respectively, led to premature discontinuation.

A summary of treatment-emergent adverse events causing withdrawal by PY is presented in **Table 15**; to be included in this table, at least 2 MedDRA events and >0.1 event per 100 PY in any treatment group, excluding the febuxostat total group, must have led to withdrawal. In addition, the following MedDRA HLTs had 1 event each in the febuxostat 80-mg and 120-mg QD groups, resulting in 2 HLT events leading to withdrawal in the febuxostat total group: Ischaemic Coronary Artery Disorders, Prostatic Neoplasms Malignant, Central Nervous System Haemorrhages and Cerebrovascular Accidents, and Headaches NEC. MedDRA HLTs with an incidence >0.2 events per 100 PY that led to premature discontinuation in the febuxostat total group were Liver Function Analyses (0.6 events per 100 PY), Renal Function Analyses

(0.3 events), Diarrhoea (Excl Infective) (0.2 events), and Urticarias (0.2 events).

Table 16 (Sponsor's Table 3.5.b). Treatment-Emergent Adverse Events by Patient-Years of Exposure (>0.1 Event Per 100 PY and >2 Events in at Least 1 Group) for Which Subjects Discontinued Study Drug in Long-Term Extension Studies

| MedDRA High Level Term MedDRA Preferred Term | Treatment Group | | | | |
|--|----------------------------------|---------------------------------|------------------------------------|------------------------------------|---|
| | Total (N=1143) (PY=1933.7) | Febuxostat | | | Allopurinol 300/100 mg QD (N=178) (PY=133.3) |
| | | 40 mg QD (N=12) (PY=33.0) | 80 mg QD (N=910) (PY=1265.4) | 120 mg QD (N=522) (PY=635.3) | |
| Number of Treatment-Emergent Adverse Events Per 100 PY That Led to Discontinuation of Study Drug | | | | | |
| Total Events | 4.4 | 6.1 | 5.0 | 3.1 | 3.0 |
| Diarrhoea (Excl Infective) Diarrhoea | 0.2 | 0 | <0.1 | 0.3 | 0 |
| Asthenic Conditions Asthenia, Fatigue | 0.1 | 0 | 0.2 | 0 | 0 |
| General Signs & Symptoms NEC Chest Discomfort, Sensation of Foreign Body | 0.1 | 0 | 0.2 | 0 | 0 |
| Pain and Discomfort NEC Non-Cardiac Chest Pain, Pain | 0.1 | 0 | 0.2 | 0 | 0 |
| Hepatocellular Damage and Hepatitis NEC Hepatic Steatosis, Hepatitis Acute | 0.1 | 0 | 0.2 | 0 | 0 |
| Liver Function Analyses Alanine Aminotransferase Increased, Aspartate Aminotransferase Increased, Hepatic Enzyme Increased, Liver Function Test Abnormal | 0.6 | 0 | 0.7 | 0.3 | 2.3 |
| Renal Function Analyses Blood Creatinine Increased, Blood Urea Increased | 0.3 | 3.0 | <0.1 | 0.5 | 0 |
| Triglyceride Analyses Blood Triglycerides Increased | 0.1 | 0 | 0.2 | 0 | 0 |
| Breathing Abnormalities Dyspnoea, Respiratory Arrest | 0.1 | 0 | 0.2 | 0 | 0 |
| Urticarias Urticaria | 0.2 | 0 | 0.2 | 0 | 0 |

PY = patient-years of exposure; NEC = not elsewhere classified
Studies included: TMC-01-005 and C02-021
Cross-reference: Statistical Table 3.1.8

Per 100 PY in the febuxostat 80-mg QD, 120-mg QD, and total febuxostat groups, 0.7 events, 0.3 events, and 0.6 events, respectively, of Liver Function Analyses led to premature discontinuation; 2.3 events per 100 PY of Liver Function Analyses led to premature discontinuation in the allopurinol 300/100-mg QD group.

Reviewer's comments:

- *This is an analysis of a partial dataset derived from ongoing open-label studies. Since this is not an analysis of a complete dataset, it can only be used for descriptive purposes. However, the following observations have been made based on presented analysis:*
- *The incidence of adverse events leading to premature discontinuation by PY was higher in the febuxostat total group (4.4 per 100 PY) than in the allopurinol group (3.0 per 100 PY). No dose response for premature discontinuation was observed between febuxostat groups.*
- *MedDRA High Level term (HLT) Liver Function Analyses was the most frequent adverse event that led to premature discontinuation and was more frequent in the allopurinol group (2.3) than in the febuxostat groups (0.6). Separate analysis of liver function tests is presented in Laboratory findings section (7.1.5) of this review.*
- *Compared to the Phase 3 randomized controlled studies, the incidence of treatment-emergent adverse events that led to premature discontinuation by PY was lower in the long-term extension studies.*
- *In addition, no change in the specific patterns of adverse events that led to premature discontinuation was noted*

7.1.3.3 Other significant adverse events

There were two deaths in phase 3 randomized controlled studies that occurred due to retroperitoneal hemorrhage in patients on concomitant warfarin and febuxostat. The approvable letter requested that the Sponsor addresses the potential for febuxostat to cause hemorrhagic events with and without co-administration of anti-coagulant.

In order to evaluate the effect of febuxostat administered with warfarin on coagulation laboratory variables, data from 2 sources are used:

- Data were captured in the clinical database through study CRFs for all Phase 3 randomized controlled and both long-term extension studies and included warfarin doses as reported by the subject and prothrombin time (PT) values measured at 3-month

intervals. Furthermore, additional available data (such as warfarin doses or PT) entered into the clinical database after the data cutoff date, are also included for completeness.

- Additional PT and international normalized ratio (INR) values drawn at outside laboratories during routine patient care, as well as additional warfarin dosing information, were obtained by TAP following the 05 December 2005 FDA meeting for subjects receiving warfarin.

The analysis is based on data from the Phase 2 and 3 clinical studies and the Phase 1 warfarin interaction study (C03-057).

Analysis of warfarin interaction study C03-057 is presented in review by Dr. Lei Zhang.

The percentage of subjects with treatment-emergent bleeding adverse events in the Phase 3 randomized controlled studies are presented for all subjects, for subjects while taking anticoagulants or antithrombotic agents, for subjects while taking warfarin, and for subjects while taking heparin in **Table 17**.

Table 17 (Sponsor's Table 3.6.qq). Number (%) of Subjects with Bleeding Adverse Events in the Phase 3 Randomized Controlled Studies

| All Subjects in Phase 3 Randomized Controlled Studies, n (%) | | | | | | |
|---|--------------------|-------------------|---------------------|----------------------|----------------------|---|
| Bleeding Adverse Events | Placebo (N=134) | Febuxostat | | | | Allopurinol 300/100 mg QD (N=521) |
| | | Total (N=1177) | 80 mg QD (N=523) | 120 mg QD (N=520) | 240 mg QD (N=134) | |
| All Events | 4 (3.0) | 55 (4.7) | 26 (5.0) | 23 (4.4) | 6 (4.5) | 21 (4.0) |
| Treatment-related Events | 1 (0.7) | 5 (0.4) | 3 (0.6) | 1 (0.2) | 1 (0.7) | 3 (0.6) |
| While Subjects were Taking Anticoagulants or Antithrombotic Agents, n (%) | | | | | | |
| Bleeding Adverse Events ^a | Placebo (N=40) | Total (N=298) | 80 mg QD (N=130) | 120 mg QD (N=125) | 240 mg QD (N=43) | 300/100 mg QD (N=107) |
| All Events | 2 (5.0) | 12 (4.0) | 7 (5.4) | 3 (2.4) | 2 (4.7) | 10 (9.3) |
| Treatment-related Events | 0 | 2 (0.7) | 1 (0.8) | 1 (0.8) | 0 | 2 (1.9) |
| While Subjects were Taking Warfarin, n (%) | | | | | | |
| Bleeding Adverse Events ^b | Placebo (N=7) | Total (N=32) | 80 mg QD (N=15) | 120 mg QD (N=15) | 240 mg QD (N=2) | 300/100 mg QD (N=12) |
| All Events | 0 | 1 (3.1) | 1 (6.7) | 0 | 0 | 1 (8.3) |
| Treatment-related Events | 0 | 0 | 0 | 0 | 0 | 1 (8.3) |
| While Subjects were Taking Heparin, n (%) | | | | | | |
| Bleeding Adverse Events ^c | Placebo (N=0) | Total (N=12) | 80 mg QD (N=6) | 120 mg QD (N=6) | 240 mg QD (N=0) | 300/100 mg QD (N=2) |
| All Events | — | 0 | 0 | 0 | — | 1 (50) |
| Treatment-related Events | — | 0 | 0 | 0 | — | 0 |

Studies included: C02-009 and C02-010

a Includes events that occurred within 7 days after taking warfarin, 3 days after taking heparin, and 1 day after taking other anticoagulants or antithrombotic agents.

b Includes events that occurred within 7 days after taking warfarin.

c Includes events that occurred within 2 days after taking heparin.

Cross-references: Statistical Tables 3.11.10.1, 3.11.10.2, 3.11.10.3, 3.11.10.4, 3.12.10.1, 3.12.10.2, 3.12.10.3 and 3.12.10.4

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Reviewer's comment:

- Overall rates of bleeding events appear to be slightly higher in febuxostat (4.7) group compared to allopurinol (4.0) and placebo (3.0) treatment groups.
- It appears that the rate of bleeding events in patients taking an anti-coagulant is higher in allopurinol group (9.3) compared to febuxostat (4.0) and placebo (5.0) groups, however as described in Table 18 below, most of those events were minor.

Bleeding adverse events (HLTs and PTs) for all subjects reported by more than 1 subject in any treatment group during the Phase 3 randomized controlled studies are summarized in Table 18.

Table 18 (Sponsor's Table 3.6.rr) Bleeding Adverse Events Reported by >1 Subject in Any Treatment Group in Phase 3 Randomized Controlled Studies

| MedDRA High Level Term MedDRA Preferred Term | Placebo (N=134) n (%) | Febuxostat | | | | Allopurinol 300/100 mg QD (N=521) n (%) |
|--|-----------------------------|----------------------------|------------------------------|-------------------------------|-------------------------------|--|
| | | Total (N=1177) n (%) | 80 mg QD (N=523) n (%) | 120 mg QD (N=520) n (%) | 240 mg QD (N=134) n (%) | |
| Total Subjects with ≥1 event | 4 (3.0) | 55 (4.7) | 26 (5.0) | 23 (4.4) | 6 (4.5) | 21 (4.0) |
| Intestinal Haemorrhages Rectal Haemorrhage | 0 | 6 (0.5) | 1 (0.2) | 3 (0.6) | 2 (1.5) | 3 (0.6) |
| Non-Site Specific Gastrointestinal Haemorrhages Gastrointestinal Haemorrhage, Haematemesis, Haematochezia | 1 (0.7) | 5 (0.4) | 4 (0.8) | 0 | 1 (0.7) | 3 (0.6) |
| Chest and Lung Injuries NEC Haemothorax | 0 | 1 (<0.1) | 1 (0.2) | 0 | 0 | 0 |
| Skin Injuries NEC Contusion | 1 (0.7) | 14 (1.2) | 4 (0.8) | 8 (1.5) | 2 (1.5) | 7 (1.3) |
| Urinary Abnormalities Haematuria | 1 (0.7) | 11 (0.9) | 6 (1.1) | 4 (0.8) | 1 (0.7) | 1 (0.2) |
| Nasal Disorders NEC Epistaxis | 0 | 4 (0.3) | 2 (0.4) | 2 (0.4) | 0 | 5 (1.0) |
| Purpura and Related Conditions Ecchymosis, Increased Tendency to Bruise, Petechiae | 0 | 6 (0.5) | 2 (0.4) | 3 (0.6) | 1 (0.7) | 1 (0.2) |
| Haemorrhages NEC Haematoma | 0 | 3 (0.3) | 2 (0.4) | 1 (0.2) | 0 | 0 |

NEC = not elsewhere classified

Cross-reference: Statistical Table 3.11.10.1

Five subjects experienced a serious or severe bleeding adverse event (2 on febuxostat 80 mg QD, 1 on febuxostat 120 mg QD, 1 on allopurinol 300 mg QD, and 1 on placebo). Four of the 5 events occurred in subjects not taking an anticoagulant or antithrombotic agent, including Subject 2745 (C02-010, febuxostat 80 mg) with an SAE of haemothorax attributed to a motor

vehicle accident that led to premature discontinuation, Subject 2426 (C02-010, febuxostat 120 mg QD) with an SAE of rectal hemorrhage attributed to hemorrhoids that was moderate in severity, Subject 2762 (C02-010, allopurinol 300 mg) with a rectal haemorrhage attributed to hemorrhoids, and Subject 4154 (C02-009, placebo) with a contusion attributed to injury. One SAE of retroperitoneal hemorrhage occurred in a subject taking febuxostat and warfarin (Subject 2019).

In the Phase 3 randomized controlled studies, warfarin was used by 7 (5%) subjects in the placebo group, 15 (3%) subjects each in the febuxostat 80-mg and 120-mg QD groups, 2 (2%) subjects in the febuxostat 240-mg QD group, and 12 (2%) subjects in the allopurinol 300/100-mg QD group.

While on warfarin, a bleeding adverse event was reported for 1 (6.7%) subject in the febuxostat 80-mg QD group (MedDRA PT: retroperitoneal hemorrhage) and 1 (8.3%) subject in the allopurinol group (MedDRA PT: epistaxis)

Table 19 (Sponsor's Table 3.6.tt). Overall Incidence Rates of Bleeding Adverse Events per 100 Patient-Years of Exposure in Long-Term Extension Studies

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| All Subjects in Long-Term Extension Studies | | | | | |
|--|----------------------------------|---------------------------------|------------------------------------|------------------------------------|--|
| Bleeding Adverse Events | Febuxostat | | | | Allopurinol |
| | Total (N=1143) (PY=1933.7) | 40 mg QD (N=12) (PY=33.0) | 80 mg QD (N=910) (PY=1265.4) | 120 mg QD (N=522) (PY=635.3) | 300/100 mg QD (N=178) (PY=133.3) |
| All Events | 3.6 | 0 | 3.6 | 3.9 | 2.3 |
| Treatment-related Events | 0.5 | 0 | 0.2 | 0.9 | 0 |
| While Subjects were Taking Anticoagulants or Antithrombotic Agents | | | | | |
| Bleeding Adverse Events ^a | Total (N=314) (PY=568.7) | 40 mg QD (N=1) (PY=4.2) | 80 mg QD (N=251) (PY=407.8) | 120 mg QD (N=119) (PY=150.6) | 300/100 mg QD (N=43) (PY=34.6) |
| | All Events | 3.9 | 0 | 4.2 | 3.3 |
| Treatment-related Events | 0.5 | 0 | 0 | 2.0 | 0 |
| While Subjects were Taking Warfarin | | | | | |
| Bleeding Adverse Events ^c | Total (N=41) (PY=76.7) | 40 mg QD (N=0) — | 80 mg QD (N=27) (PY=47.6) | 120 mg QD (N=19) (PY=28.2) | 300/100 mg QD (N=8) (PY=6.9) |
| | All Events | 3.9 | — | 4.2 | 3.6 ^b |
| Treatment-related Events | 1.3 ^b | — | 0 | 3.6 ^b | 0 |
| While Subjects were Taking Heparin | | | | | |
| Bleeding Adverse Events ^d | Total (N=30) (PY=48.1) | 40 mg QD (N=0) — | 80 mg QD (N=20) (PY=31.6) | 120 mg QD (N=11) (PY=14.7) | 300/100 mg QD (N=3) (PY=3.7) |
| | All Events | 2.1 ^b | — | 0 | 6.8 ^b |
| Treatment-related Events | 2.1 ^b | — | 0 | 6.8 ^b | 0 |

Studies included: TMX-01-005 and C02-021

- a Includes events that occurred within 7 days after taking warfarin, 2 days after taking heparin, and 1 day after taking other anticoagulants or antithrombotic agents.
 b This represents 1 subject (Subject 4756) who started warfarin and heparin for treatment of lacunar infarction the day of the event.
 c Includes events that occurred within 7 days after taking warfarin.
 d Includes events that occurred within 2 days after taking heparin.

Cross-references: Statistical Tables 3.9.10.5, 3.9.10.6, 3.9.10.7, 3.9.10.8, 3.10.10.5, 3.10.10.6, 3.10.10.7 and 3.10.10.8

Reviewer's comment:

- As in Phase 3 randomized controlled studies, in long-term extension studies the overall rate of bleeding events is slightly higher in febuxostat group (3.6) compared to allopurinol group (2.3).
- When anti-coagulant is co-administered, the rate of bleeding events is higher in allopurinol group (5.8) compared to febuxostat group (3.9). As presented in Table 20 below, most of the bleeding events were minor.

Bleeding adverse events with an incidence >0.1 per 100 PY in the febuxostat total group in the long-term extension studies are summarized in Table 20.

Table 20 (Sponsor's Table 3.6.uu). Bleeding Adverse Events (>0.1 Per 100 PY in Febuxostat Total Group) in Long-Term Extension Studies

| MedDRA High Level Term MedDRA Preferred Term | Febuxostat | | | | Allopurinol |
|---|----------------------------------|---------------------------------|------------------------------------|------------------------------------|--|
| | Total (N=1143) (PY=1933.7) | 40 mg QD (N=12) (PY=33.0) | 80 mg QD (N=910) (PY=1265.4) | 120 mg QD (N=522) (PY=635.3) | 300/100 mg QD (N=178) (PY=133.3) |
| Number of Subjects with Bleeding Events Per 100 PY | | | | | |
| Total Subjects with ≥1 event | 3.6 | 0 | 3.6 | 3.9 | 2.3 |
| Thrombocytopenias Idiopathic Thrombocytopenic Purpura, Thrombocytopenia | 0.2 | 0 | 0.2 | 0 | 0 |
| Ocular Bleeding and Vascular Disorders NEC Eye Haemorrhage | 0.2 | 0 | 0.2 | 0.2 | 0 |
| Intestinal Haemorrhages Rectal Haemorrhage | 0.3 | 0 | 0.3 | 0.3 | 0.8 |
| Non-Site Specific Gastrointestinal Haemorrhages Haematemesis, Haematochezia | 0.2 | 0 | <0.1 | 0.3 | 0 |
| Skin Injuries NEC Contusion | 1.1 | 0 | 1.3 | 0.8 | 1.5 |
| Urinalysis NEC Blood Urine Present | 0.2 | 0 | 0.2 | 0 | 0 |
| Urinary Abnormalities Haematuria | 0.8 | 0 | 0.5 | 1.4 | 0 |
| Nasal Disorders NEC Epistaxis | 0.4 | 0 | 0.5 | 0.2 | 0 |
| Purpura and Related Conditions Echymosis, Petechiae, Purpura | 0.2 | 0 | 0.2 | 0.2 | 0 |
| Haemorrhages NEC Haematoma | 0.2 | 0 | 0.2 | 0.3 | 0 |

PY = patient-years of exposure; NEC = not elsewhere classified
Cross-reference: Statistical Table 3.9.10.5

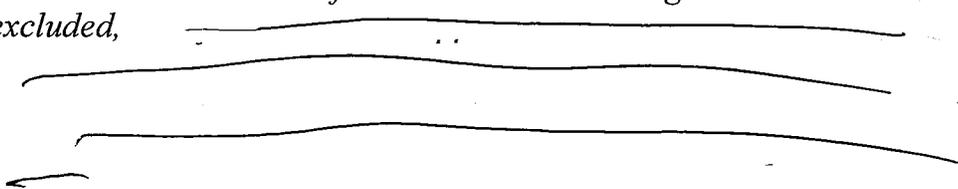
Four subjects had serious adverse events, all of which were severe. Two of the subjects were not taking anticoagulants: Subject 2823 (C02-021, febuxostat 120 mg), a 50-year-old male with cerebral hemorrhage in the left basal ganglia attributed to hypertension, and Subject 4598 (C02-021, febuxostat 80 mg), a 49-year-old male with idiopathic thrombocytopenic purpura and associated epistaxis and purpura.

Serious adverse events in subjects taking an anticoagulant or antithrombotic agent were reported in 2 subjects: Subject 4756 (C02-021, febuxostat 120 mg), a 51-year-old male who had a history of cerebrovascular accident and was taking aspirin and clopidogrel, experienced lacunar infarction and remains ongoing in the study. Subject 4186 (death due to retroperitoneal hemorrhage), who was taking febuxostat concomitantly with warfarin and Lovenox.

In addition, 2 subjects experienced non-serious bleeding adverse events that led to premature

discontinuation. Subject 4709 (C02-021, febuxostat 120 mg) had haematochezia and haematuria attributed to Vioxx and was not taking an anticoagulant or antithrombotic. Subject 1180 (TMX-01-005, febuxostat 120 mg) had rectal haemorrhage attributed to colon polyps and was taking aspirin.

Reviewer's comments:

- *Since the number of patients in each group taking concomitant anti-coagulants is very small, no definitive conclusions can be drawn.*
- *It does appear that the incidence of bleeding events increases slightly in all groups when concomitant anticoagulant is added. No evidence of a dose response was noted.*
- *Two serious adverse bleeding events in patients taking concomitant anti-coagulant occurred in febuxostat group. Two patients died from retroperitoneal hemorrhage while on concomitant febuxostat and warfarin. In addition, one non-serious AE of rectal hemorrhage in a patient on concomitant febuxostat and warfarin/aspirin led to a study discontinuation.*
- *The interaction between febuxostat and anti-coagulants cannot be excluded,*


- *By doing the re-analysis, the Sponsor has addressed the issue in the approvable letter*

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7.1.4 Common Adverse Events

Long-term extension studies

In the febuxostat total group, the 10 most common treatment-emergent adverse events included the following MedDRA preferred terms: upper respiratory tract infection, nasopharyngitis, arthralgia, headache, back pain, diarrhoea, sinusitis, hypertension, pain in extremity, and influenza. These adverse events have been previously reported in the original ISS and 4-Month Safety Update as common adverse events and are similar to events reported for allopurinol. The incidence of these events was generally similar between the febuxostat 80-mg and 120-mg QD treatment groups.

Table 21 (Sponsor's Table 3.2.a). Most Frequently Reported (>5 HLT Events per 100 PY)

Clinical Review
Tatiana Oussova, MD, MPH
NDA 21-856/S-01
Uloric/febuxostat tablets 80 mg and 120 mg

Treatment-Emergent Adverse Events by Patient-Years of Exposure in Long-Term Extension Studies

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

| MedDRA High Level Term MedDRA Preferred Term | Treatment Group | | | | |
|--|----------------------------------|---------------------------------|------------------------------------|------------------------------------|---|
| | Febuxostat | | | | Allopurinol 300/100 mg QD (N=178) (PY=133.3) |
| | Total (N=1143) (PY=1933.7) | 40 mg QD (N=12) (PY=33.0) | 80 mg QD (N=910) (PY=1265.4) | 120 mg QD (N=512) (PY=635.3) | |
| Number of Treatment-Emergent Events Per 100 PY | | | | | |
| Total Events | 228.6 | 269.8 | 242.1 | 199.7 | 207.8 |
| Upper Respiratory Tract Infections Acute Sinusitis, Chronic Sinusitis, Laryngitis, Nasopharyngitis, Pharyngitis, Rhinitis, Sinusitis, Tonsillitis, Upper Respiratory Tract Infection | 26.8 | 30.3 | 27.6 | 25.2 | 23.3 |
| Musculoskeletal and Connective Tissue Signs and Symptoms NEC Back Pain, Buttock Pain, Chest Wall Pain, Flank Pain, Limb Discomfort, Musculoskeletal Chest Pain, Musculo- skeletal Discomfort, Musculoskeletal Stiffness, Neck Pain, Pain in Extremity, Sacral Pain, Shoulder Pain | 13.4 | 12.1 | 13.9 | 12.6 | 15.0 |
| Joint Related Signs and Symptoms Arthralgia, Joint Crepitation, Joint Effusion, Joint Range of Motion Decreased, Joint Stiffness, Joint Swelling | 9.4 | 3.0 | 9.5 | 9.4 | 8.3 |
| Headaches NEC Headache, Sinus Headache, Tension Headache | 8.6 | 0 | 9.0 | 8.3 | 5.3 |
| Lower Respiratory Tract and Lung Infections Bronchial Infection, Bronchiectasis, Bronchitis, Bronchitis Acute, Bronchitis Chronic, Bronchopneumonia, Lobar Pneumonia, Lower Respiratory Tract Infection, Lung Infection, Pneumonia, Pneumonia Primary Atypical | 6.0 | 6.1 | 6.6 | 4.9 | 4.5 |
| Diarrhoea (Excl Infective) Diarrhoea | 4.7 | 9.1 | 4.0 | 5.8 | 2.3 |

PY = patient-years of exposure; NEC = not elsewhere classified

Studies included: TMX-01-005 and C02-021

Note: Most frequent events include HLTs with at least 5 events per 100 patient-years (prior to rounding) in at least 1 dose group.

Cross-references: Statistical Tables 3.1.1 and 3.1.3

| MedDRA High Level Term MedDRA Preferred Term | Treatment Group | | | | |
|---|----------------------------------|---------------------------------|------------------------------------|------------------------------------|---|
| | Febuxostat | | | | Allopurinol 300/100 mg QD (N=178) (PY=133.3) |
| | Total (N=1143) (PY=1933.7) | 40 mg QD (N=12) (PY=33.0) | 80 mg QD (N=910) (PY=1265.4) | 120 mg QD (N=322) (PY=635.3) | |
| Number of Treatment-Emergent Events Per 100 PY | | | | | |
| Vascular Hypertensive Disorders NEC Hypertension | 4.5 | 9.1 | 4.5 | 4.2 | 3.8 |
| Influenza Viral Infections Influenza | 3.9 | 12.1 | 4.3 | 2.7 | 0.8 |
| Paraesthesias and Dysaesthesias Burning Sensation, Hypoaesthesia, Paraesthesia, Post Herpetic Neuralgia | 3.2 | 18.2 | 3.2 | 2.4 | 2.3 |
| Tendon Disorders Ganglion, Tendon Disorder, Tendonitis, Trigger Finger | 2.2 | 6.1 | 2.6 | 1.1 | 3.0 |
| Asthenic Conditions Asthenia, Fatigue, Malaise | 1.7 | 9.1 | 1.3 | 2.0 | 1.5 |
| Renal Lithiasis Nephrolithiasis | 1.5 | 9.1 | 1.4 | 1.3 | 1.5 |
| Hyperlipidaemias NEC Hyperlipidaemia | 1.4 | 12.1 | 1.4 | 0.9 | 0.8 |
| Depressive Disorders Depression | 0.9 | 9.1 | 0.7 | 0.8 | 1.5 |
| Renal Function Analyses Blood Creatinine Increased, Blood Urea Increased | 0.9 | 9.1 | 0.9 | 0.5 | 1.5 |
| Bladder and Urethral Symptoms Dysuria, Incontinence, Micturition Disorder, Micturition Urgency, Pollakiuria, Urinary Hesitation, Urinary Incontinence, Urinary Retention | 0.8 | 6.1 | 0.9 | 0.5 | 0 |
| External Ear Disorders NEC Cerumen Impaction | 0.3 | 6.1 | 0.2 | 0 | 0 |

PY = patient-years of exposure; NEC = not elsewhere classified

Studies included: TMCX-01-005 and C02-021

Note: Most frequent events include HLTs with at least 5 events per 100 patient-years (prior to rounding) in at least 1 dose group.

Cross-references: Statistical Tables 3.1.1 and 3.1.3

Compared to the Phase 3 randomized controlled trials, the overall incidence of treatment-emergent adverse events, as well as the incidence of frequently reported adverse events, was lower in the long-term extension studies.

Reviewer's comments:

In the long-term extension studies:

- *Common treatment-emergent adverse events were similar to those previously reported for febuxostat and similar to events reported for allopurinol in the original ISS and 4-Month Safety Update.*
- *Compared to the Phase 3 randomized controlled studies, the overall incidence of treatment-emergent adverse events, as well as the incidence of frequently reported adverse events, was lower in the long-term extension studies.*

7.1.5 Laboratory Findings

In the long-term extension studies, small mean changes from baseline to each visit were observed for various chemistry parameters. These changes were similar across treatment groups and none were considered to be clinically relevant.

The proportions of subjects with shifts to low or high for chemistry parameters were generally comparable in the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100-mg QD groups.

Statistically significant differences between the allopurinol 300/100-mg QD and the febuxostat 80-mg QD and/or 120-mg QD groups were observed for shifts to high in sodium, chloride, BUN, albumin, and magnesium; and shifts to low and high in bicarbonate. These statistically significant differences may have been due to the greater exposure and therefore greater number of visits during which laboratory evaluations were performed in the febuxostat groups than in the allopurinol group.

Of note, creatine phosphokinase (CPK) was only assessed in TMX-01-005, which did not include an allopurinol control group.

Potentially concerning chemistry laboratory values are summarized in **Table 22**.

Table 22 (Sponsor's Table 4.2.b). Potentially Concerning Chemistry Laboratory Values in Long-Term Extension Studies

| Variable (Potentially Concerning Criteria) | Febuxostat | | | Allopurinol |
|---|--|---|---|---|
| | 40 mg QD N=12 (PY=33.0) n/N (%) | 80 mg QD N=910 (PY=1265.4) n/N (%) | 120 mg QD N=522 (PY=635.3) n/N (%) | 300/100 mg QD N=178 (PY=133.3) n/N (%) |
| Sodium | | | | |
| Low (≤ 124 mEq/L) | 0/12 | 1/893 (<1) | 0/505 | 0/173 |
| High (≥ 151 mEq/L) | 0/12 | 12/893 (1) | 4/505 (<1) | 0/173 |
| Potassium | | | | |
| Low (≤ 2.9 mEq/L) | 0/12 | 2/893 (<1) | 1/504 (<1) | 0/173 |
| High (≥ 5.9 mEq/L) | 0/12 | 10/893 (1) | 3/504 (<1) | 3/173 (2) |
| Bicarbonate | | | | |
| Low (≤ 17 mEq/L) | 8/12 (67) | 43/893 (5) | 18/505 (4) | 2/173 (1) |
| Glucose | | | | |
| Low (≤ 49 mg/dL) | 0/12 | 2/893 (<1) | 2/505 (<1) | 0/173 |
| High (≥ 301 mg/dL) | 1/12 (8) | 8/893 (<1) | 4/505 (<1) | 0/173 |
| BUN | | | | |
| High (≥ 31 mg/dL) | 4/12 (33) | 86/893 (10) | 37/505 (7) | 9/173 (5) |
| Creatinine | | | | |
| High (≥ 1.5 mg/dL and increased from baseline by ≥ 0.3 mg/dL) | 1/12 (8) | 76/893 (9) | 26/505 (5) | 8/173 (5) |
| Inorganic Phosphorus | | | | |
| Low (≤ 1.5 mg/dL) | 0/12 | 1/893 (<1) | 1/503 (<1) | 0/173 |
| High (≥ 9.0 mg/dL) | 0/12 | 1/893 (<1) | 0/503 | 0/173 |
| Albumin | | | | |
| Low (≤ 2.4 g/dL) | 0/12 | 1/893 (<1) | 0/505 | 0/173 |
| Total Bilirubin | | | | |
| High (≥ 2.0 mg/dL) | 0/12 | 17/893 (2) | 4/505 (<1) | 0/173 |
| Alkaline Phosphatase | | | | |
| High ($\geq 2 \times$ ULN) | 0/12 | 1/893 (<1) | 0/504 | 0/173 |
| AST | | | | |
| High ($\geq 2 \times$ ULN) | 0/12 | 65/893 (7) | 38/504 (8) | 8/173 (5) |
| ALT | | | | |
| High ($\geq 2 \times$ ULN) | 3/12 (25) | 105/893 (12) | 54/504 (11) | 17/173 (10) |
| GGT | | | | |
| High ($\geq 3 \times$ ULN) | 1/12 (8) | 6/114 (5) | 3/34 (9) | -- |
| CPK | | | | |
| High ($\geq 3 \times$ ULN) | 1/12 (8) | 14/114 (12) | 7/34 (21) | -- |
| Total Cholesterol | | | | |
| High (≥ 350 mg/dL and increased from baseline by ≥ 100 mg/dL) | 0/12 | 8/893 (<1) | 4/505 (<1) | 1/173 (<1) |
| Triglyceride | | | | |
| High ($\geq 2 \times$ ULN and increased from baseline by ≥ 100 mg/dL) | 6/12 (50) | 123/893 (14) | 69/505 (14) | 10/173 (6) |

ULN = upper limit of normal

Studies included: TMX-01-005 and C02-021

Note: Table includes only those chemistry parameters with at least one non-zero category.

Cross-reference: Statistical Tables 4.3 and 4.4

Reviewer's comment:

- Increase in BUN, total bilirubin, AST and ALT occurs at slightly higher rates in febuxostat groups compared to allopurinol group

- *This is consistent with previous observations from phase 3 randomized studies*

Analyses of shifts in hepatic parameters in the long-term extension studies are summarized in **Table 23**.

Table 23 (Table 3.6.jj). Shifts in Hepatic Parameters Relative to Normal Range in Long-Term Extension Studies

| | Febuxostat | | | Allopurinol |
|-----------------------------|-------------------------------|--------------------------------|---------------------------------|-------------------------------------|
| | 40 mg QD (N=12) n/N (%) | 80 mg QD (N=910) n/N (%) | 120 mg QD (N=522) n/N (%) | 300/100 mg QD (N=178) n/N (%) |
| Total Bilirubin | | | | |
| Shift to High | 0/12 | 52/870 (6) | 27/490 (6) | 5/173 (3) |
| Shift to Low | 0/12 | 31/885 (4) | 21/500 (4) | 5/172 (3) |
| Alkaline Phosphatase | | | | |
| Shift to High | 2/11 (18) | 62/874 (7) | 21/494 (4) | 14/171 (8) |
| Shift to Low | 0/12 | 6/887 (<1) | 1/502 (<1) | 1/171 (<1) |
| AST | | | | |
| Shift to High | 5/10 (50) | 274/778 (35) | 155/445 (35) | 44/157 (28) |
| Shift to Low | 0/12 | 2/893 (<1) | 3/503 (<1) | 0/173 |
| ALT | | | | |
| Shift to High | 5/6 (83) | 274/685 (40) | 162/397 (41) | 43/136 (32) |
| Shift to Low | 0/12 | 2/893 (<1) | 0/504 | 2/173 (1) |

Cross-reference: Statistical Table 4.2.1

In order to provide better comparison between groups, the Sponsor performed analysis of shifts in hepatic laboratory variables by time interval. In this analysis, during the 12 months to <18 months interval, a statistically significantly higher proportion of subjects in the febuxostat 120-mg QD group than in the allopurinol 300/100-mg QD group shifted to high AST (24% [35/148] vs. 8% [3/40], p=0.026) and to high ALT (34% [47/137] vs. 9% [3/32]; p=0.005).

The proportions of subjects with shifts appeared to decrease over time.

Table 24 (Table 3.6.kk). Proportions of Subjects with Elevated Liver Function Test Values in the Long-Term Extension Studies

| Hepatic Chemistry Parameter Elevation Criterion | Treatment Group n/N (%) | | | |
|--|-------------------------|---------------------|----------------------|---|
| | Febuxostat | | | Allopurinol 300/100 mg QD (N=178) |
| | 40 mg QD (N=12) | 80 mg QD (N=910) | 120 mg QD (N=522) | |
| ALT | | | | |
| ≥2×Upper Limit of Normal | 3/12 (25) | 105/893 (12) | 54/504 (11) | 17/173 (10) |
| ≥3×Upper Limit of Normal | 1/12 (8) | 29/893 (3) | 18/504 (4) | 4/173 (2) |
| ≥5×Upper Limit of Normal | 0/12 | 3/893 (<1) | 1/504 (<1) | 2/173 (1) |
| ≥10×Upper Limit of Normal | 0/12 | 2/893 (<1) | 0/504 | 0/173 |
| AST | | | | |
| ≥2×Upper Limit of Normal | 0/12 | 65/893 (7) | 38/504 (8) | 8/173 (5) |
| ≥3×Upper Limit of Normal | 0/12 | 16/893 (2) | 12/504 (2) | 3/173 (2) |
| ≥5×Upper Limit of Normal | 0/12 | 3/893 (<1) | 1/504 (<1) | 3/173 (2) |
| ≥10×Upper Limit of Normal | 0/12 | 1/893 (<1) | 1/504 (<1) | 0/173 |
| ALT and AST Concurrently | | | | |
| ≥2×Upper Limit of Normal | 0/12 | 47/893 (5) | 27/504 (5) | 7/173 (4) |
| ALT ≥2×ULN and Total Bilirubin | | | | |
| ≥2 mg/dL Concurrently | 0/12 | 2/893 (<1) | 0/504 | 0/173 |
| AST ≥2×ULN and Total Bilirubin | | | | |
| ≥2 mg/dL Concurrently | 0/12 | 2/893 (<1) | 0/504 | 0/173 |

ULN = Upper Limit of Normal

Studies included: TMX-01-005 and C02-021

Cross-reference: Statistical Table 4.6

No new subjects since the 4-Month Safety Update had an ALT >5·ULN, an ALT or AST >2·ULN concurrent with a total bilirubin value >2.0 mg/dL, or an ALT or AST >2·ULN concurrent with alkaline phosphatase >2·ULN. One new subject in the febuxostat 120-mg QD group (Subject 4485) had an AST >5·ULN. This subject experienced an increase in AST from 56 to 391 U/L and in ALT from 44 to 151 U/L on a single occasion. Two weeks later, AST and ALT were 75 and 44 U/L, respectively. No adverse event was reported, and the subject continued in the study without reoccurrence.

Reviewer’s comments:

In long-term extension studies:

- *The incidence of increased total bilirubin is 6% in each of febuxostat groups and 3% in allopurinol group. In the original ISS and 4-Month Safety Update, an increased incidence of LFT elevations was observed with treatment with febuxostat 80 mg QD or febuxostat 120 mg QD when compared to placebo or allopurinol. The concern was raised during initial review cycle about febuxostat potential for hepatotoxicity. Additional analysis provided by the Sponsor supports the previously raised concern.*

- *No dose response was noted, and no case of severe liver injury was observed in the febuxostat program.*

7.2 Adequacy of Patient Exposure and Safety Assessments

See original NDA review

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The clinical development program for febuxostat in the United States includes a total of 2531 subjects who have received at least one dose of febuxostat across the Phase 1, 2 and 3 trials. Except for 2 ongoing, long-term extension studies (TMX-01-005 and C02-021), all studies were completed and previously reported in the NDA. This safety update includes an additional 12 months of safety data since the 4-Month Safety Update. As of 16 November 2005, approximately 900 subjects were ongoing in the long-term extension studies.

Due to study design, the majority of subjects in Studies TMX-01-005 and C02-021 were treated with febuxostat 80 mg QD or febuxostat 120 mg QD, the doses proposed for registration. Therefore, exposure is greater in the febuxostat 80-mg QD and febuxostat 120-mg QD dose groups as compared to the allopurinol 300/100-mg QD group for this safety update. The mean cumulative exposure during the long-term extension studies was 618 days for subjects treated with febuxostat and 274 days for subjects treated with allopurinol. Of note, there has been no additional exposure to placebo and to febuxostat 240 mg QD.

In order to adjust for differences in duration of exposure among treatment groups in the long-term extension studies, adverse events were summarized by patient-years of exposure (PY) in this safety update. As the Phase 3 randomized studies were fully reported in the original NDA, the only new analyses presented for these studies are those conducted to address cardiovascular safety and the potential for hemorrhagic events when febuxostat is administered with anticoagulants. Cardiovascular events and bleeding events in the long-term extension studies are also summarized by percentage of subjects with an event without adjustment for exposure. No clinically relevant differences were noted between groups for demographic variables in the long-term extension studies, and the demographic characteristics of the subjects were comparable to those of the Phase 3 randomized controlled studies.

All-Cause Mortality and Cardiovascular Mortality

There were 12 deaths in febuxostat arms compared to zero in allopurinol. 10 out of 12 deaths were adjudicated by the Sponsor as APTC events. The all-cause mortality rate in febuxostat group was highest in Phase 3 controlled studies (0.60) and somewhat less in long-term studies (0.43). Of note, the same trend was noticed for other adverse events. One plausible explanation

for this is that a subgroup of the most vulnerable patients dropped out of the study during the blinded phase due to either death or adverse event.

Cardiovascular deaths occurred at a rate of 0.45 per 100 PY in phase 3 controlled studies and at 0.36 per 100 PY in long-term extension studies. The incidence of cardiovascular deaths in the allopurinol group is 0.

Cardiovascular Adverse Events

Multiple analyses were done for Phase 3 randomized controlled studies, Phase 2/3 randomized controlled studies, and long-term extension studies, to assess potential cardiovascular toxicity with febuxostat treatment.

Long-term treatment with febuxostat appears to have an untoward effect on the cardiovascular system and increases the frequency of cardiovascular adverse events when compared to allopurinol.

Criteria established by the Anti-Platelet Trialists' Collaboration (APTC) were applied in an analysis of investigator-reported events by identifying MedDRA Preferred Terms corresponding to the APTC criteria. This analysis included primary APTC events (CV death and non-fatal myocardial infarction, stroke, and cardiac arrest) and secondary APTC events (angina, revascularization, TIA, venous and peripheral arterial vascular thrombotic events and non-fatal CHF). Additional cardiovascular analyses were performed after adjudication by a consulting cardiologist hired by the Sponsor blinded to treatment and study. However, there are a number of limitations to such an analysis.

- First of all, it was done post hoc after the data were already analyzed. In addition, no attempts to collect incomplete data could be made making the adjudication of a number of adverse events difficult.
- It was done by a single Sponsor-hired cardiologist versus a group of independent adjudicators.

As a part of the analysis, the Sponsor included certain events such as CHF and revascularization into a group of thrombotic events. Those events in most cases are not thrombotic in nature, but inclusion of those events in the group of true thromboembolic events could potentially dilute the true risk of thrombotic events.

The percentages of subjects with investigator-reported, treatment-emergent primary APTC events and primary and secondary APTC events in the Phase 3 randomized controlled studies and long-term extension studies were consistently higher in the febuxostat 80-mg and 120-mg QD groups than the allopurinol group. There was no apparent evidence of a dose response between febuxostat groups. The incidence rates of different individual non-adjudicated primary APTC events in phase 3 controlled studies is three to four times higher in febuxostat group compared to allopurinol group; the incidence rates of different individual non-adjudicated primary and secondary APTC events (more inclusive) in phase 3 controlled studies is three times higher in febuxostat group compared to allopurinol group.

For the adjudicated analysis of APTC events in the Phase 3 controlled study and Phase 2/3 controlled study grouping, the combined incidence of CV death, non-fatal myocardial infarction, and stroke as well as the incidence of individual events was higher in the febuxostat treatment groups when compared to placebo and allopurinol. No dose response was observed. The incidence rates of different individual adjudicated primary APTC events in phase 3 controlled studies is two to three times higher in febuxostat group compared to allopurinol group.

The number of subjects reporting treatment-emergent cardiovascular adverse events per 100 PY was lower during the long-term extension studies compared to the Phase 3 randomized controlled studies but this could be due to depletion of susceptible sub-population.

In the long-term extension studies analyzed by exposure, the combined incidence of CV death, non-fatal myocardial infarction, and stroke as well the incidence of individual events was higher in the febuxostat treatment groups compared to allopurinol.

The incidence rates of different individual non-adjudicated primary APTC events (myocardial infarction and stroke) in long-term extension studies is two times higher in febuxostat group compared to allopurinol group when adjusted for the difference in exposure.

The incidence rates of different individual adjudicated primary APTC events in long-term extension studies is 1.5 to two times higher in febuxostat group compared to allopurinol group when adjusted for the difference in exposure.

Even though cardio-vascular adverse events are expected in the general population, and more so in a population of patients with gout due to multiple CV risk factors, one cannot assume those events are due to underlying disease or intercurrent illness, and not the drug. Thus, a comparison with a control group is very important. In this case, the comparator drug is allopurinol with the mechanism of action similar to that of febuxostat. There were no differences in background characteristics between the two groups. Therefore, any difference in efficacy results or safety profile that is seen between the two drugs can be attributed to the drug itself. Comparison between febuxostat and allopurinol suggests that there is an excess risk of all-cause mortality and cardiovascular mortality among patients who took febuxostat. This difference in risk persists after differences in exposure are taken into account. No dose-related increases in cardio-vascular events were observed on febuxostat.

The findings in these analyses are consistent with previous finding in original NDA. Review of the Sponsor's **adjudicated** cardiovascular adverse events that occurred during phase 3 controlled studies does not change the conclusion reached by this reviewer in original NDA review.

These reanalyses confirmed the unfavorable risk/benefit profile of febuxostat in regard to cardiovascular adverse events compared to allopurinol in a population that had no apparent differences in baseline characteristics.

Bleeding Events/Interactions with Anticoagulants

Since the number of patients in each group taking concomitant anti-coagulants is very small, no definitive conclusions can be drawn.

It does appear that the incidence of bleeding events increases slightly in all groups when concomitant anticoagulant is added. No evidence of a dose response was noted.

Though most of the bleeding events were minor and non-serious in patients taking concomitant febuxostat and warfarin, two serious adverse bleeding events occurred. Two patients died from retroperitoneal hemorrhage while on concomitant febuxostat and warfarin. In addition one non-serious AE of rectal hemorrhage in a patient on concomitant febuxostat and warfarin/aspirin led to a study discontinuation.

The interaction between febuxostat and anti-coagulants cannot be excluded,

b(4)

Of note, in long-term extension studies the incidence of increased total bilirubin is 6% in each of febuxostat groups and 3% in allopurinol group. No dose response was noted, and no case of severe liver injury was observed in the febuxostat program. In the original ISS and 4-Month Safety Update, an increased incidence of LFT elevations was observed with treatment with febuxostat 80 mg QD or febuxostat 120 mg QD when compared to placebo or allopurinol. The concern was raised during initial review cycle about febuxostat potential risk for liver toxicity. Additional analysis provided by the Sponsor does not eliminate the previously raised concern.

Conclusions

Alternative analyses provided by the Sponsor in this submission did not suggest a substantially different conclusion. This reviewer concludes that these new analyses did not eliminate the concern that there is a strong trend toward increased risk of cardio-vascular events in patients treated with febuxostat.

As was mentioned earlier in this review, randomized controlled studies are viewed as the gold-standard for evidence-based decisions. Since the studies conducted by the Sponsor were not designed as safety studies and therefore were relatively small and short in duration, the number of serious adverse events causing concerns is expected to be small. The open label studies are able to strengthen or confirm suspected risks raised by controlled studies but usually are not sufficient to eliminate it completely. Much larger outcome safety studies would be needed to provide a more robust assessment of the safety of this product.

In this submission, additional data included into analyses came from open-label studies and did support a conclusion reached in original reviews, even when discrepancy in exposure between treatment groups is factored into an analyses.

The increased risk of cardiovascular events persists in patients treated with febuxostat compared to placebo or active comparator allopurinol. Since the treatment groups were balanced in terms of background characteristics including pre-existing medical conditions, such an increase in risks cannot be explained by the fact that the population has multiple pre-existing cardio-vascular illnesses predisposing them to new cardio-vascular events.

The drug has been shown to be efficacious in reducing the level of uric acid in hyperuricemic patients with gout however this is only a surrogate endpoint recommended by the Advisory Committee. In addition to showing efficacy in uric acid reduction, the clinical benefits should be evident as well.

7.4 General Methodology

7.4.1 Explorations for time dependency for adverse findings

Analysis of APTC by Onset Date

Time of Onset analysis for Primary APTC Events in the Phase 3 Randomized Controlled Studies is presented in Table 25.

Table 25 (Sponsor's Table 3.6.i). Percentage of Subjects with Investigator Reported Primary APTC Events by Onset Date in the Phase 3 Randomized Controlled Studies

| Interval | Treatment Group, n/N (%) | | | | |
|------------------|--------------------------|---------------------|----------------------|----------------------|---|
| | Placebo (N=134) | Febuxostat | | | Allopurinol 300/100 mg QD (N=521) |
| | | 80 mg QD (N=523) | 120 mg QD (N=520) | 240 mg QD (N=134) | |
| 0 to <3 Months | 0/134 (0.0) | 1/523 (0.2) | 2/520 (0.4) | 0/134 (0.0) | 0/521 (0.0) |
| 3 to <6 Months | 0/111 (0.0) | 2/424 (0.5) | 1/425 (0.2) | 0/96 (0.0) | 0/452 (0.0) |
| 6 to <9 Months | 0/101 (0.0) | 0/372 (0.0) | 0/376 (0.0) | 0/87 (0.0) | 1/420 (0.2) |
| 9 to <12 Months | - | 1/179 (0.6) | 2/161 (1.2) | - | 0/193 (0.0) |
| 12 to <15 Months | - | 0/159 (0.0) | 0/141 (0.0) | - | 0/181 (0.0) |

Studies included: C02-009 and C02-010
Cross-reference: Statistical Table 3.5.4.1

Reviewer's comments:

- *Time-of-onset analyses for investigator-reported primary APTC events in the Phase 3 randomized controlled studies suggests that there might be an increase in event over time (9-12 months of exposure) in febuxostat group. However, interpretation of this analysis is very difficult due to small number of events in each group.*

Time of Onset for Primary and Secondary APTC in the Phase 3 Randomized Controlled Studies

Analyses of investigator-reported treatment-emergent primary and secondary APTC events by onset date in the Phase 3 randomized controlled studies are summarized in Table 26.

Table 26 (sponsor's Table 3.6.j). Percentage of Subjects with Investigator Reported Primary and Secondary APTC Events by Onset Date in the Phase 3 Randomized Controlled Studies

| Interval | Treatment Group, n/N (%) | | | | |
|------------------|--------------------------|---------------------|----------------------|----------------------|---|
| | Placebo (N=134) | Febuxostat | | | Allopurinol 300/100 mg QD (N=521) |
| | | 80 mg QD (N=523) | 120 mg QD (N=520) | 240 mg QD (N=134) | |
| 0 to <3 Months | 1/134 (0.7) | 6/523 (1.1) | 6/520 (1.2) | 1/134 (0.7) | 3/521 (0.6) |
| 3 to <6 Months | 0/111 (0.0) | 5/424 (1.2) | 1/425 (0.2) | 0/96 (0.0) | 1/452 (0.2) |
| 6 to <9 Months | 0/101 (0.0) | 3/372 (0.8) | 2/376 (0.5) | 0/87 (0.0) | 3/420 (0.7) |
| 9 to <12 Months | - | 1/179 (0.6) | 3/161 (1.9) | - | 0/193 (0.0) |
| 12 to <15 Months | - | 0/159 (0.0) | 0/141 (0.0) | - | 0/181 (0.0) |

Studies included: C02-009 and C02-010
 Cross-reference: Statistical Table 3.5.4.2

Reviewer's comments:

- *Time-of-onset analyses for investigator-reported primary and secondary APTC events in the Phase 3 randomized controlled studies suggests that there might be an increase in event over time (9-12 months of exposure) in febuxostat group.*
- *It seems that there is no increase in event over time in allopurinol group. However, interpretation of this analysis is very difficult due to small number of events in each group.*

Time of Onset for Primary APTC Events for the Long-Term Extension Studies

Analyses of investigator-reported treatment-emergent primary APTC events by onset date in the long-term extension studies are summarized in Table 27.

Table 27 (Sponsor's Table 3.6.k). Percentage of Subjects with Investigator-Reported Primary APTC Events by Onset Date in Long-Term Extension Studies

| Interval | Treatment Group, n/N (%) | | | |
|------------------|--------------------------|---------------------|----------------------|---|
| | Febuxostat | | | Allopurinol 300/100 mg QD (N=178) |
| | 40 mg QD (N=12) | 80 mg QD (N=910) | 120 mg QD (N=522) | |
| 0 to <3 Months | 0/12 (0.0) | 2/910 (0.2) | 2/522 (0.4) | 0/178 (0.0) |
| 3 to <6 Months | 0/10 (0.0) | 3/740 (0.4) | 0/422 (0.0) | 0/111 (0.0) |
| 6 to <9 Months | 0/10 (0.0) | 2/630 (0.3) | 2/366 (0.5) | 0/83 (0.0) |
| 9 to <12 Months | 0/8 (0.0) | 2/593 (0.3) | 2/337 (0.6) | 1/61 (1.6) |
| 12 to <15 Months | 0/8 (0.0) | 3/577 (0.5) | 2/317 (0.6) | 0/58 (0.0) |
| 15 to <18 Months | 0/8 (0.0) | 4/548 (0.7) | 0/297 (0.0) | 0/53 (0.0) |
| 18 to <21 Months | 1/8 (12.5) | 4/517 (0.8) | 1/264 (0.4) | 0/51 (0.0) |
| 21 to <24 Months | 0/8 (0.0) | 1/413 (0.2) | 1/169 (0.6) | 0/33 (0.0) |
| 2 to <3 Years | 0/8 (0.0) | 0/246 (0.0) | 0/20 (0.0) | 0/2 (0.0) |
| 3 to <4 Years | 0/7 (0.0) | 0/44 (0.0) | 0/12 (0.0) | - |
| 4 to <5 Years | 0/7 (0.0) | 0/41 (0.0) | 0/11 (0.0) | - |

Studies included: TMX-01-005 and C02-021

For events that occurred after the dose/drug switches, the onset date was the date relative to the start of dose/drug switches

Cross-reference: Statistical Table 3.3.4.1

Subjects with the same adverse event in more than 1 time interval are counted in each of these time intervals. The percentage of subjects with a primary APTC event in any particular 3-month interval did not increase over time. Also, events were not clustered in the initial treatment interval in the long-term extension studies.

Reviewer's comments:

- *Though the number of events in each group is small, and the analysis of these data is difficult to interpret, it appears that the number of events in febuxostat group might increase over time with exposure between 12-24 months. Studies are ongoing and the data are being collected and therefore the analysis of completed dataset would be needed.*

8 OVERALL ASSESSMENT

8.1 Conclusions

The efficacy of 80 mg and 120 mg doses of febuxostat was established during the initial review cycle and was based on a surrogate end-point. However, this reviewer concludes that the new analyses provided with this resubmission did not eliminate the concern raised during initial review cycle that the apparent signal of increased risk of cardiovascular thromboembolic adverse events among patients treated with febuxostat is not predictive of clinically important differences.

Based on a review of reanalyses of data provided with this resubmission, febuxostat doses 80 mg and 120 mg should not be approved.

9.2 Recommendation on Regulatory Action

Non-approvable action is recommended by the reviewer for febuxostat 80 mg and 120 mg tablets for the treatment of hyperuricemia associated with gout.

9.4 Labeling Review

Was not completed due to non-approvable action

9.5 Comments to Applicant

The Sponsor should be advised on the following options:

- To evaluate lower doses of febuxostat. An additional trial of febuxostat 40 mg dose coupled with Japanese data might provide a sufficient database to evaluate an efficacy and a safety.
- Additionally, studying febuxostat in a subgroup of patients intolerant to allopurinol might prove to be beneficial to this population.
- Should the Sponsor insist on continuing evaluating the safety profile of febuxostat 80 mg and 120 mg, a cardio-vascular outcome study evaluating febuxostat safety with allopurinol as a comparator should be required.
- It was noted that the number of events in febuxostat group might increase over time with exposure between 12-24 months. An analysis of the completed dataset would be needed to assess this observation further.
- A long term clinical study should also be performed to verify whether the reduction in the uric acid level is associated with important clinical benefits such as reduction in a number of gout flares.

10 APPENDICES

APPENDIX 1

Table 3.4.d Subjects With Other Newly Reported or Updated Serious Adverse Events Since the 4-Month Safety Update

| Study No./Phase | Subject/Age/Gender | Adverse Event (MedDRA Preferred Term) ^a | Relationship to Study Drug | Day of Onset ^b | Duration (Days) ^c | D/C | Comment ^d |
|--------------------------------|--------------------|--|----------------------------|---------------------------|------------------------------|-----------|---|
| Febuxostat 40 mg | | | | | | | |
| TMX-01-005/2 | 1152/66/Male | Pneumonia ^a | Not related | 586 [614] | 5 | No | Alternative etiologies: bacterial pneumonia, hypertensive disease, bacterial pneumonia, spondylitis, and inflamed gallbladder, respectively |
| | | Cerebrovascular Accident ^a | Not related | 686 [714] | 4 | No | |
| | | Pneumonia ^a | Not related | 783 [811] | 5 | No | |
| | | Lumbar Spinal Stenosis ^a | Not related | 1097 [1125] | 3 | No | |
| | | Cholecystitis ^a | Not related | 1371 [1399] | 7 | No | |
| Febuxostat 80 mg | | | | | | | |
| TMX-01-005/2 | 1007/73/Female | Osteoarthritis | Unlikely | 1700 [1728] | 5 | No | Alternative etiology: elective knee replacement due to worsening of osteoarthritis of left knee. |
| TMX-01-005/2 | 1021/65/Male | Atrial Fibrillation | Not related | 1589 [1616] | 2 | No | Alternative etiology: dehydration; subject also on colchicine at time of event. |
| TMX-01-005/2 | 1032/74/Female | Rotator Cuff Syndrome ^a | Unlikely | 567 [595] | 38 | No | Alternative etiology: bacterial |
| | | Osteoporotic Fracture ^a | Not related | 669 [697] | 19 | No | |
| | | Exacerbation ^a | Not related | 842 [870] | 70 | No | |
| | | Urosepsis ^a | Unlikely | 1457 [1485] | 9 | No | |
| TMX-01-005/2 | 1055/49/Male | Prostate Cancer ^a | Unlikely | 1231 [1258] | Ong (1512) | Yes | Alternative etiology: genetic predisposition. Narrative updated with postoperative PSA results and last day of study drug. |
| Febuxostat 80 mg (Cont) | | | | | | | |
| TMX-01-005/2 | 1122/73/Male | Benign Lung Neoplasm ^a | Unlikely | 327 [356] | 53 | No | Alternative etiologies: probable old pulmonary etiology, bacterial, and history of heart disease, respectively. Pneumonia narrative updated to include relevant hospital laboratory information and to indicate MI was ruled out. Atrioventricular Block reported as Arrhythmia in the original ISS, but term was updated in the 4-Month Safety Update. |
| | | Pneumonia ^a | Not related | 948 [977] | 5 | No | |
| | | Atrioventricular Block 2nd Degree ^a | Not related | 1073 [1102] | 6 | No | |
| TMX-01-005/2 | 1165/69/Female | Divericulitis ^a | Not related | 852 [880] | 3 | No | Alternative etiologies: bacterial infection, abdominal adhesions, and probable diverticulitis, respectively |
| | | Small Intestinal Obstruction ^a | Not related | 1210 [1238] | 3 | No | |
| | | Radiation Injury ^a | Unlikely | 1453 [1481] | 6 | No | |
| C02-010/3 | 2024/77/Male | Cardiac Failure Congestive ^a | Not related | 248 | 46 | No | International Normalised Ratio (INR) increased narrative updated with coumatin dosing information and additional INR and prothrombin time results. |
| | | Renal Failure Acute ^a | Not related | 248 | 46 | No | |
| | | International Normalised Ratio Increased ^a | Not related | 272 | 22 | No | |
| C02-009/3 C02-021/3 | 4775/65/Male | Transient Ischaemic Attack ^a | Not related | 60 | <1 | No | Alternative etiologies: arterial stenosis and genetic, respectively, for the CAD events. Subject received febuxostat 120 mg QD Days 1-36 in Study C02-021. |
| | | Coronary Artery Disease ^a | Not related | 281 [477] | 2 | No | |
| | | Coronary Artery Disease | Not related | 500 [696] | 29 | No | |
| C02-021/3 | 2004/64/Male | Myocardial Infarction ^a Ventricle Rupture ^a | Not related Not related | 158 [502] 143 [507] | 5 10 | No No | Alternative etiology: cardiac history. Myocardial Infarction narrative updated to include study drug information for C02-010. |
| Febuxostat 80 mg (Cont) | | | | | | | |
| C02-021/3 | 2655/70/Female | Cerebrovascular Accident ^a | Unlikely | 465 [833] | 50 | Yes | Alternative etiology: hypertension. Narrative updated to include relevant family history, MRI results, and information on insertion of carotid artery stent. |
| C02-021/3 | 2662/72/Male | Hemiparesis ^a | Possible | 433 [799] | 5 min | No | Alternative etiologies: cerebral atherosclerosis (for both Hemiparesis and Electroencephalogram [EEG] Abnormal) and arteriosclerosis with thrombosis for Pulmonary Embolism. Hemiparesis/EEG narrative updated to include alternative etiology and follow-up EEG information. |
| | | Electroencephalogram Abnormal ^a Pulmonary Embolism | Possible Unlikely | 434 [800] 676 [1042] | 2 4 | No Yes | |
| C02-021/3 | 2119/70/Male | Carotid Artery Stenosis | Not related | 655 [1021] | 2 | No | Alternative etiology: hyperlipidemia |
| C02-021/3 | 3131/76/Male | Aortic Valve Stenosis Postpericardiectomy Syndrome | Not related Not related | 609 [974] 624 [999] | 6 Ong (754) | No No | Alternative etiologies: possible valvular heart disease and status-post aortic valve repair |
| C02-010/3 C02-021/3 | 2199/65/Male | Coronary Artery Disease ^a | Not related | 112 | 3 | No | Subject received allopurinol 300/100 mg QD in Study C02-010. Alternative etiologies for Iron Deficiency Anemia and Colonic Polyp: idiopathic colonic polyps and idiopathic, respectively. |
| | | Iron Deficiency Anemia | Not related | 478 [946] | 4 | No | |
| | | Colonic Polyp | Not related | 505 [875] | 6 | No | |

Clinical Review
Tatiana Oussova, MD, MPH
NDA 21-856/S-01
Uloric/Febuxostat tablets 80 mg and 120 mg

| Study No./Phase | Subject/Age/Gender | Adverse Event (MedDRA Preferred Term)* | Relationship to Study Drug | Day of Onset* | Duration (Days)* | D/C | Comment* |
|--------------------------------|--------------------|---|---|-------------------------------------|------------------|----------------|---|
| Febuxostat 80 mg (Cont) | | | | | | | |
| C02-021/3 | 2294/37/Male | Pneumonia Cholecystitis Pneumonia | Not related Not related Not related | 504 [867] 508 [871] 548 [911] | 13 135 18 | No No No | Alternative etiologies: virus, abnormal gallbladder, and bacterial, respectively |
| C02-021/3 | 2316/40/Male | Angina Pectoris | Unlikely | 701 [1070] | 3 | No | Alternative etiology: coronary artery disease |
| C02-021/3 | 2365/67/Male | Sinusitis | Not related | 566 [931] | 2 | No | Alternative etiology: infection |
| C02-021/3 | 2377/44/Male | Myocardial Infarction | Not related | 557 [919] | 4 | No | Alternative etiology: complication during ablation |
| C02-021/3 | 2454/83/Male | Cellulitis Osteomyelitis | Not related Not related | 375 [746] 486 [857] | 85 3 | No No | Alternative etiologies: bacterial skin infection and bone infection, respectively |
| C02-021/3 | 2483/62/Male | Cholelithiasis* Cholecystitis | Not related Not related | 383 [747] 383 [747] | 5 5 | No No | Alternative etiologies: preexisting condition and cholelithiasis, respectively. Cholelithiasis narrative updated to change investigator assessment of causality from unlikely to not related and to include SAE term of Cholecystitis. |
| C02-021/3 | 2520/46/Male | Osteoarthritis | Not related | 514 [876] | 2 | No | Alternative etiology: degenerative joint disease |
| Febuxostat 80 mg (Cont) | | | | | | | |
| C02-010/3 | 2658/66/Female | Syncope* | Not related | 260 | 4 | No | Alternative etiology: concurrent illness for all events. Updated alternative etiologies in CIOMS but not yet captured in clinical database are HCTZ therapy for Hypokalaemia and Hyponatremia and acute dehydration/volume depletion for Syncope and Renal Failure. |
| C02-021/3 | | Hypokalaemia | Not related | 684 [1045] | 5 | No | |
| | | Hyponatremia | Not related | 684 [1045] | 5 | No | |
| | | Renal Failure | Not related | 684 [1045] | 5 | No | |
| | | Syncope | Not related | 684 [1045] | 5 | No | |
| C02-021/3 | 2673/53/Male | Urinary Tract Infection | Not related | 684 [1045] | Unknown | No | |
| C02-021/3 | 2673/53/Male | Pulmonary Embolism Deep Vein Thrombosis | Unlikely Unlikely | 434 [798] 434 [798] | 5 5 | No No | Alternative etiology: multiple episodes of night knee effusions for both events |
| C02-010/3 | 2686/67/Male | Ventricular Extrasystoles* | Not related | 171 | Ong (495) | No | Subject received allopurinol in Study C02-010. Alternative etiology for Coronary Artery Disease (CAD): cholesterol deposition. CAD narrative updated to indicate subject developed nonserious congestive heart failure and underwent coronary artery bypass graft; cardiac echo information also added. |
| C02-021/3 | | Coronary Artery Disease* | Not related | 245 [609] | 13 | No | |
| C02-021/3 | 2790/85/Male | Cerebrovascular Accident | Possible | 627 [987] | 10 | No | Alternative etiology: history of hypertension |
| C02-021/3 | 2852/52/Male | Diverticulitis* | Not related | 250 [616] | 70 | No | Alternative etiology: diverticulosis. Narrative updated to include information on readministration of study drug, colon resection, and imaging. |
| C02-021/3 | 4064/55/Male | Myocardial Infarction | Not related | 481 [677] | 11 hours | No | Alternative etiology: underlying cardiac disease |
| Febuxostat 80 mg (Cont) | | | | | | | |
| C02-021/3 | 4066/44/Male | Cholecystitis Acute Procedural Complication | Not related Not related | 553 [749] 557 [751] | 14 9 | Yes Yes | Alternative etiologies: cholecystitis and surgical bile clipping, respectively |
| C02-021/3 | 4097/70/Female | Breast Cancer Recurrent [Breast Cancer In Situ] | Not related | 665 [891] | Ong (666) | Yes | MedDRA term in brackets is an updated term in the CIOMS that is not yet in the clinical database. Alternative etiology: recurrent breast cancer. |
| C02-021/3 | 4112/70/Male | Atherosclerosis Colitis Ischaemic | Not related Not related | 582 [776] 600 [794] | 1 5 | No No | Alternative etiologies: increased triglycerides, smoking, hypertension, and recent vascular surgery, respectively |
| C02-021/3 | 4172/51/Male | Syncope | Unlikely | 623 [819] | 1 | No | Alternative etiology: possible vasovagal response |
| C02-021/3 | 4205/49/Male | Cellulitis | Not related | 461 [657] | 35 | No | Alternative etiology: spider bite |
| C02-021/3 | 4245/74/Male | Cerebrovascular Accident Carotid Artery Stenosis | Unlikely Not related | 544 [740] 559 [755] | 7 1 | No No | Alternative etiologies: underlying atherosclerotic cerebrovascular disease and atherosclerotic carotid artery disease |
| C02-021/3 | 4303/63/Male | Acute Myocardial Infarction | Not related | 521 [715] | 9 | Yes | Alternative etiology: hypertension |
| C02-009/3 | 4308/68/Male | Atrial Fibrillation* | Unlikely | 127 | 7 | No | Subject received febuxostat 120 mg in Study C02-009. He started on allopurinol in Study C02-021; switched to febuxostat 80 mg on Day 132. |
| C02-021/3 | | Cardiac Failure Congestive* | Not related | 104 [295] | 5 | No | |
| C02-021/3 | | Dizziness | Not related | 403 [594] | 1 minute | No | |
| C02-021/3 | 4315/56/Male | Angina Unstable* | Unlikely | 288 [489] | Ong (329) | No | Alternative etiology: underlying coronary artery disease. Narrative updated to indicate vessels of the left coronary system normal. |

| Study No./Phase | Subject/Age/Gender | Adverse Event (MedDRA Preferred Term) ^a | Relationship to Study Drug | Day of Onset ^b | Duration (Days) ^c | D/C | Comment ^d |
|--------------------------------|--------------------|--|----------------------------|---------------------------|------------------------------|-----|---|
| Febuxostat 80 mg (Cont) | | | | | | | |
| C02-021/3 | 4409/57/Male | Acute Myocardial Infarction | Not related | 402 [598] | 5 | No | Alternative etiologies: history of cardiac disease with stent prior to randomization and bacterial infection for Acute Myocardial Infarction (MI) and Pneumonia, respectively, and coronary artery disease for Chest Pain and both MI on Days 541 and 643. |
| | | Pneumonia | Not related | 523 [719] | 6 | No | |
| | | Acute Myocardial Infarction | Not related | 541 [737] | 6 | No | |
| | | Chest Pain | Not related | 596 [792] | 6 | No | |
| | | Myocardial Infarction | Not related | 643 [839] | 25 | No | |
| C02-021/3 | 4445/45/Male | Abdominal Strangulated Hernia | Not related | 558 [754] | 7 | No | Alternative etiology: secondary to muscle strain |
| C02-021/3 | 4529/43/Female | Osteoarthritis | Not related | 554 [749] | Ong (639) | Yes | Alternative etiology: osteoarthritis. The CIOMS report lists the event as arthralgia, but updated information in the clinical database indicates that the event was osteoarthritis. |
| C02-021/3 | 4598/49/Male | Idiopathic Thrombocytopenia Purpura ^e | Probable | 117 [313] | 16 | Yes | Subject took allopurinol before changing to febuxostat on Day 71. In vitro platelet aggregation and activation studies revealed that febuxostat-treated serum did not induce platelet aggregation or cause significant platelet activation. Narrative updated with study drug start/stop dates. |
| Febuxostat 80 mg (Cont) | | | | | | | |
| C02-021/3 | 4641/49/Male | Angina Pectoris ^f | Not related | 134 [327] | 2 | No | Alternative etiologies: coronary artery disease and dehydration due to diuretic, respectively. Angina Pectoris originally reported as Cardiac Stress Test Abnormal in original ISS, but term was updated in the 4-Month Safety Update. Hypotension SAB captured in CIOMS and not yet captured in clinical database; all information presented for this event is from CIOMS. |
| | | Renal Failure Acute ^g | Not related | 178 [371] | Ong (304) | No | |
| | | Hypotension | Not related | 533 [726] | 6 | No | |
| C02-021/3 | 4736/60/Male | Myocardial Infarction | Not related | 552 [746] | 5 | No | Alternative etiology: coronary artery disease |
| C02-021/3 | 4821/69/Male | Coronary Artery Disease | Not related | 578 [774] | 2 | No | Alternative etiologies: coronary artery disease and urinary tract infection, respectively. |
| | | Urosepsis | Not related | 580 [776] | 5 | No | |

D/C = discontinuation due to the serious adverse event; Ong = ongoing; AE = adverse event

Note: For subjects in Study TMX-01-005, age is at time of entry in Study TMX-00-004. For subjects in Study C02-021, age is at time of entry in Study C02-009 or C02-010.

Note: Subjects are categorized by treatment received during the most recent adverse event that occurred during the long-term extension study.

- a The terms in bold are the new SAEs that were reported since the 4-Month Safety Update. MedDRA Preferred Terms with recent dictionary updates are shown by the previous term here and are shown by the updated term in the CIOMS.
- b Number in brackets represents the cumulative study days since the first dose of study drug in Studies C02-009, C02-010, or TMX-00-004. Day of onset may vary slightly between the clinical database and the CIOMS; the days reported here are from the clinical database, unless otherwise noted.
- c AE was ongoing as of study day in parentheses; duration is in days unless otherwise noted.
- d Information derived from Tables 3.4d and 3.4e of the original ISS and Tables 3.4.c and 3.4.d of the 4-Month Safety Update for previously reported events. Otherwise, alternative etiology is provided for new events or those updated since the 4-Month Safety Update.
- e Event previously reported in the original ISS.
- f Event previously reported in the 4-Month Safety Update.
- g Event first reported in the original ISS; updated information reported in the 4-Month Safety Update.
- h Event first reported in the 4-Month Safety Update; updated information.
- i Event first reported in the original ISS; updated information reported in the 4-Month Safety Update; updated information since the 4-Month Safety Update.
- j Event previously reported in the original ISS; updated information.

Cross-references: Statistical Tables 7.2.1 and 7.3 and TAP Pharmacovigilance database

| Study No./Phase | Subject/Age/Gender | Adverse Event (MedDRA Preferred Term) ^a | Relationship to Study Drug | Day of Onset ^b | Duration (Days) ^c | D/C | Comment ^d |
|--------------------------------|--------------------|--|----------------------------|---------------------------|------------------------------|-----|--|
| Febuxostat 80 mg (Cont) | | | | | | | |
| C02-021/3 | 4839/54/Male | Incisional Hernia | Not related | 354 [547] | 3 | No | Alternative etiology: secondary to previous hernia repair |
| C02-021/3 | 4895/74/Male | Myocardial Infarction ^a | Unlikely | 157 [352] | 32 | No | Alternative etiologies: CAD, post-operative complication, PAD, and postoperative infection, respectively. Myocardial Infarction narrative updated with event of Post Procedural Complication and corresponding imaging results. |
| | | Post Procedural Complication | Unlikely | 170 [365] | 19 | No | |
| | | Peripheral Vascular Disorder | Not related | 563 [758] | Ong (613) | No | |
| | | Postoperative Infection | Not related | 595 [790] | Ong (613) | No | |
| C02-021/3 | 4916/47/Male | Cerebrovascular Accident ^b | Unlikely | 256 [464] | 104 | No | Alternative etiologies: hypertension and diabetes. Narrative updated to indicate CT scan was unremarkable. |
| C02-021/3 | 4959/71/Male | Cardiac Failure Congestive ^c | Not related | 13 [215] | 3 | No | Alternative etiologies: prior condition, bacterial infection, congestive heart failure, underlying disease progression, and coronary artery disease, respectively. Death due to cardiac failure congestive, cardiorespiratory arrest, and respiratory failure (Table 3.3.c). |
| | | Pneumonia ^d | Not related | 13 [215] | 3 | No | |
| | | Coronary Artery Disease | Not related | 256 [458] | 115 | No | |
| | | Cardiac Failure Congestive | Not related | 256 [458] | 115 | No | |
| | | Myocardial Infarction | Not related | 358 [560] | 7 | No | |
| C02-021/3 | 6002/81/Male | Fall | Not related | 441 [637] | 7 | No | Alternative etiology: mechanical fall |
| C02-021/3 | 6017/64/Male | Myocardial Infarction | Not related | 423 [628] | Unknown | No | Alternative etiologies: preexisting atherosclerotic cardiovascular disease and underlying cardiac disease, respectively. |
| | | Coronary Artery Disease | Not related | 423 [628] | 10 | No | |

Clinical Review
 Tatiana Oussova, MD, MPH
 NDA 21-856/S-01
 Uloric/Februxostat tablets 80 mg and 120 mg

| Study No./Phase | Subject/Age/Gender | Adverse Event (MedDRA Preferred Term) ^a | Relationship to Study Drug | Day of Onset ^b | Duration (Days) ^c | D/C | Comment ^d |
|----------------------------------|--------------------|--|---|--|------------------------------|----------------------------|--|
| Februxostat 120 mg | | | | | | | |
| C02-021/3 | 2050/47/Male | Colonic Polyp | Not related | 382 [948] | 5 | No | Alternative etiology: unknown/genetic |
| C02-021/3 | 2214/38/Male | Nephrolithiasis ^e | Unlikely | 433 [799] | 29 | No | Alternative etiology: history of stress. Narrative updated to indicate subject fully recovered. |
| C02-021/3 | 2519/62/Female | Non-Small Cell Lung Cancer | Not related | 549 [920] | 1 | Yes | Alternative etiology: primary lung cancer. |
| C02-021/3 | 2578/69/Male | Aortic Aneurysm Peripheral Artery Aneurysm Femoral Artery Aneurysm Colitis Ischaemic | Not related Not related Not related Not related | 555 [923] 647 [1015] 647 [1015] 680 [1048] | 102 63 63 8 | No No No No | Alternative etiology: history of cardiovascular (CV) disease for first aneurysm, arteriosclerotic heart disease (ASHD) and coronary artery bypass graft for second and third aneurysms, and medical history of CV disease with recent stent placements for Colitis Ischaemic. Aortic Aneurysm and Colitis Ischaemic were reported in the CIOMS but not yet entered in the Clinical database. Day of onset and duration for these events were calculated based on information in the TAP PV database. |
| C02-021/3 | 2602/58/Male | Vertigo | Not related | 555 [905] | 4 | No | Alternative etiology: dehydration |
| Februxostat 120 mg (Cont) | | | | | | | |
| C02-010/3 C02-021/3 | 2610/62/Male | Anal Fibrosis ^g Osteoarthritis ^g Osteoarthritis ^g Osteoarthritis ^g Osteoarthritis ^g | Not related Not related Not related Not related Not related | 317 63 [420] 206 [563] 477 [834] 623 [980] | 4 2 hours 5 2 5 | No No No No No | Alternative etiologies: CAD, DJD (degenerative joint disease), osteoarthritis (OA). For the first 2 OA events, MedDRA PT was reported as Localised OA in the original ISS and 4-Month Safety Update, but the term was changed to OA when MedDRA was updated from version 7.1 to 8.0. The fourth event of OA was reported in the CIOMS but not yet entered in the clinical database; all information presented for this event is from CIOMS/PV database. |
| C02-021/3 | 2616/50/Male | Pulmonary Granuloma | Not related | 276 [644] | 357 | No | Alternative etiology: probable yeast infection - possible histoplasmosis |
| C02-021/3 | 2825/50/Male | Cerebral Haemorrhage | Not related | 376 [744] | 26 | Yes | Alternative etiology: hypertension |
| C02-010/3 | 2865/52/Male | Cardiac Failure Congestive ^g | Not related | 51 | 7 | No | Subject also had SAE of Cardiac Failure Congestive prior to starting study drug. |
| C02-021/3 | | Cardiac Failure Congestive ^g | Not related | 211 | 4 | No | Alternative etiology: preexisting condition |
| C02-021/3 | 4043/44/Male | Lobar Pneumonia | Unlikely | 434 [804] | 8 | No | Alternative etiology: community acquired |
| C02-021/3 | | | | 429 [626] | 13 | No | Alternative etiology: community acquired |
| Februxostat 120 mg (Cont) | | | | | | | |
| C02-021/3 | 4186/84/Female | Chronic Obstructive Airways Disease Exacerbated ^h Atrial Fibrillation ^h Fluid Overload ^h | Not related Not related Not related | 406 [602] 406 [602] 406 [602] | 27 27 27 | No No No | Alternative etiologies: history of COPD, arrhythmia common with COPD, and new-onset atrial fibrillation, respectively. Death due to retroperitoneal haemorrhage (Table 3.3.c). Narrative updated to indicate subject developed left lower lobe pneumonia and tachybrady arrhythmia and subsequently severe hypotension; warfarin was held due to increased INR, and autopsy report indicated arrhythmia as cause of death. INR and partial thromboplastin time (PTT) results were added. |
| C02-021/3 | 4302/51/Male | Coronary Artery Disease | Not related | 443 [637] | 2 | No | Alternative etiology: atherosclerosis |
| C02-021/3 | 4329/50/Male | Myocardial Infarction ⁱ Myocardial Infarction | Not related Not related | 204 [404] 568 [768] | 3 5 | No No | Alternative etiology: cardiac history for both events. Myocardial infarction Day 204 narrative updated with ECG, cardiac catheterization, and cardiac echo information. |
| C02-021/3 | 4351/72/Male | Oesophageal Carcinoma | Not related | 500 [697] | 64 | Yes | Alternative etiology: chronic GERD |
| C02-021/3 | 4503/38/Male | Cellulitis | Unlikely | 578 [776] | 5 | No | Alternative etiology: skin infections |
| C02-021/3 | 4516/52/Male | Cerebrovascular Accident | Not related | 650 [846] | Ong (674) | No | Alternative etiology: cardiac risk factors for stroke (updated to hypertension in CIOMS but not yet captured in clinical database). |

Clinical Review
 Tatiana Oussova, MD, MPH
 NDA 21-856/S-01
 Uloric/febuxostat tablets 80 mg and 120 mg

| Study No./Phase | Subject/Age/Gender | Adverse Event (MedDRA Preferred Term)* | Relationship to Study Drug | Day of Onset ^b | Duration (Days) ^c | D/C | Comment ^d |
|----------------------------------|--------------------|---|--|--|------------------------------|----------------------|---|
| Febuxostat 120 mg (Cont) | | | | | | | |
| C02-021/3 | 4757/60/Male | Intervertebral Disc Protrusion | Not related | 346 [546] | 12 hours | No | Alternative etiology: back strain |
| C02-021/3 | 4753/52/Male | Cardiac Failure Congestive ^e Diabetes Mellitus Non-Insulin Dependent ^f | Unlikely Unlikely | 250 [443] 304 [496] | 10 8 | No No | Alternative etiology: uncontrolled hypertension and steroid precipitated concomitant infection, respectively. Switched from allopurinol to febuxostat on Day 35. Diabetes narrative updated to add investigator assessment of causality and nonsensous AE of hemia. |
| C02-021/3 | 4756/59/Male | Transient Ischaemic Attack ^g Lacunar Infarction | Unlikely Possible | 271 [467] 492 [688] | 3 Ong (549) | No No | Alternative etiologies: multiple comorbid conditions, including obesity, hypertension, and dyslipidemia. Transient Ischaemic Attack narrative updated to indicate change from previously reported term of stroke. |
| Febuxostat 120 mg (Cont) | | | | | | | |
| C02-021/3 | 4776/74/Male | Coronary Artery Disease Diverticulitis Diverticulitis Atrial Fibrillation | Not related Not related Not related Not related | 349 [461] 513 [725] 595 [807] 604 [816] | 10 3 Ong (621) 7 | No No No No | Alternative etiologies: genetic, bacterial infection, infection (and recurrence of diverticulitis, as updated in CIOMS but not yet in clinical database), and coronary heart disease, respectively. The event of Atrial Fibrillation was reported in the CIOMS but not yet entered in the clinical database; all information presented is from CIOMS. |
| C02-021/3 | 4887/56/Male | Coronary Artery Occlusion | Not related | 478 [672] | 2 | No | Alternative etiology: hyperlipidemia (updated to coronary artery disease in CIOMS but not yet captured in clinical database). |
| C02-021/3 | 4915/65/Male | Osteoarthritis | Not related | 384 [578] | 28 | No | Alternative etiology: degenerative arthritis |
| C02-021/3 | 5016/32/Male | Intervertebral Disc Protrusion | Not related | 388 [484] | 2 | No | Alternative etiology: degenerative |
| C02-021/3 | 5027/46/Male | Appendicitis | Not related | 449 [644] | 2 | No | Alternative etiology: bacterial infection |
| Allopurinol 300/100 mg QD | | | | | | | |
| C02-021/3 | 4180/58/Male | Cervicobrachial Syndrome | Not related | 615 [806] | 87 | No | Alternative etiology: history of cervical radiculopathy |
| C02-021/3 | 4653/56/Male | Atrial Fibrillation | Not related | 358 [568] | 5 | No | Alternative etiology: electrical conduction defect |
| C02-021/3 | 4811/76/Male | Myocardial Infarction | Unlikely | 281 [508] | 22 | No | Alternative etiology: CAD |
| C02-021/3 | 4955/62/Male | Spinal Column Stenosis | Not related | 316 [512] | 4 | No | Alternative etiology: degenerative spinal process |

APPENDIX 2

The cardio-renal consult is reproduced below.

Date: May 12, 2006

From: Thomas A. Marciniak, M.D.

Medical Team Leader

Division of Cardiovascular and Renal Products (HFD-110)

Subject: Cardiovascular events with febuxostat, NDA 21-856

Through: Norman Stockbridge, M.D., Ph.D.

Division Director

To: Matthew Sullivan

Division of Anesthesia, Analgesia and Rheumatology Products (HFD-170)

This memo responds to your consult to us dated April 10, 2006, requesting that we perform a blinded adjudication of cardiovascular events in thirteen cases from the febuxostat development program. We have provided a brief summary of the adjudication criteria and a table with our

adjudications, followed by some comments on the adjudication.

Case Adjudication

The material you provided claims that the assessments performed by the sponsor's consultant were based on the Antiplatelet Trialists' Collaboration (APTC) endpoints excluding GI hemorrhage (Antiplatelet Trialists' Collaboration 1994). The endpoints adjudicated were the following: (1) cardiac events – arrhythmias, acute coronary syndromes, angina pectoris, cardiac arrest, coronary revascularization including percutaneous transluminal angioplasty or coronary artery bypass graft surgery, congestive heart failure (HF), and acute myocardial infarction (MI); (2) deaths, including sudden/unexplained death or other cardiac death; and (3) cerebrovascular events – carotid stenosis or carotid revascularization, ischemic or hemorrhagic stroke, syncope, and transient ischemic attack. The following definitions were used for certain events: Acute myocardial infarction was defined as the presence of two of the following criteria: (1) chest pain or equivalent of a cardiac nature; (2) any abnormal value of creatine phosphokinase MB or troponin; (3) myocardial injury pattern or development of Q waves in two contiguous electrocardiographic leads. Stroke was defined as an acute, focal neurologic event lasting > 24 hours, with imaging studies used if available. Cardiovascular death was defined as sudden or explained death or those due to myocardial infarction, stroke, or pulmonary embolus. If the clinical data supported a different diagnosis from that of the original reporter, the event was reclassified. If the data available were insufficient to make a definitive diagnosis, then the original reporter's diagnosis was accepted. When two events that were clinically linked occurred within 1-2 weeks of each other, only the more severe event was included—e.g., a stroke followed by death from stroke was analyzed only as a cardiovascular death. We show our adjudications in the table below.

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Table: Adjudication of Events for 13 Patients in the Febuxostat Development Progra

| # | Study day ¹ | Event | Adequate info ² | Comment |
|------|------------------------|--------------------------------|----------------------------|---|
| 310 | 3 | CV death | Yes | Sudden death |
| 2019 | 49 | Worsening HF | Yes | |
| | 161 | Worsening HF | No | Per investigator |
| | 287 | Non-CV death | Yes | Retroperitoneal bleed |
| 2223 | 313 | MI | No | Per investigator |
| | 314 | Coronary revasc ³ | No | Angioplasty |
| 2403 | 169 | Carotid revasc | Yes | |
| | 170 | CV death | Yes | Cardiac arrest post-op |
| 2487 | 81 | Worsening HF | No | In setting of respiratory & renal failure |
| 2790 | 628 | Stroke | No | MRI diagnosed |
| 4186 | 406 | Atrial arrhythmia | Yes | New onset atrial fib |
| | 417 | Atrial arrhythmia ³ | Yes | Tachybrady syndrome |
| | 432 | Non-CV death | Yes | Retroperitoneal bleed |
| 4479 | 12 | CV death | No | Sudden death, inadequate info on MI |
| 4665 | 21 | (None) | No | Hypoglycemic seizure; troponin leak |
| 4730 | 552 | MI | No | Per investigator |
| | 552 | Coronary revasc ³ | No | Stent placement |
| 4959 | 13 | Worsening HF | Yes | With pneumonia, inadequate info for HF |
| 4963 | 84 | MI | No | Per investigator |
| | 84 | Coronary revasc ³ | No | Coronary stent |
| 5000 | 185 | MI | Yes | |

CV = cardiovascular; HF = heart failure; MI = myocardial infarction; revasc = revascularization

¹Study day of current study; patients may have been treated in earlier studies

²Whether information provided was adequate to apply criteria or otherwise confirm event

³Less serious or second of related events

Comments

The material provided did not provide complete definitions or diagnostic criteria for most events. In particular, congestive heart failure (HF) is a chronic disease, not an event. We interpreted this term to mean new onset of HF or acute exacerbation of existing HF. Also, arrhythmias are mentioned without any definition or discussion of the types of arrhythmias. We have qualified arrhythmias that we adjudicated as atrial arrhythmias—there were no documented ventricular arrhythmias reported in these cases (although, of course, the cardiac arrests probably represent ventricular arrhythmias.)

We found these adjudications to be largely an exercise in futility: Between lacking criteria for most events and lacking clinical information for most criteria, we do not consider these

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adjudications to be very helpful. For example, of the five possible MI events (six counting the sudden death attributed to an MI), for only one did the case report form provide sufficient information on all three MI criteria categories to adjudicate the event—and even that case remains arguable. For most cases we followed the adjudication rule that, if there was insufficient information to change the diagnosis, we accepted the investigator's diagnosis.

While reliable adjudication of these cases is not possible with the case report forms provided, we think that precise adjudication is not needed. The case report forms provide reasonable documentation that these events were serious and, for all but one (case 4665), that they were cardio/cerebrovascular in nature. We believe that you should count them as we have classified them in the table above for any initial evaluations of the cardiovascular safety of febuxostat. We have one additional set of comments: While the sponsor refers to their criteria as "APTC" criteria, we find little in common with the original APTC definitions. The APTC definitions used for the original APTC meta-analysis were terms for thromboembolic and bleeding events used to provide some commonality among the many endpoints used in the studies included in the meta-analysis. The APTC group was unable to specify optimal, detailed criteria (because the supporting data were not collected prospectively), to collect more information on the cases, or even to re-adjudicate them—the APTC group was forced by practicality to accept the diagnoses used in the original studies. The sponsor has extended the APTC endpoints into many other domains (e.g., arrhythmias, revascularization, and heart failure) and provided more detailed and updated criteria for some events, e.g., MI. These extensions (and more!) are appropriate and are needed to make the adjudication useful for an analytic situation in which one can examine the individual patient case reports. The criteria as provided remain too ambiguous for adjudication of most of the events, and we would not attach any credibility to them because the sponsor has labeled them as "APTC". While the criteria are weak, the larger problem remains the lack of detail in the case report forms.

Recommendations

Please see the Table above for our recommendations on classifying the 13 cases.

Reference

Antiplatelet Trialists' Collaboration (1994). "Collaborative overview of randomised trials of antiplatelet therapy Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients." *BMJ* 308(6921): 81-106.

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Clinical Review
Tatiana Oussova, MD, MPH
NDA 21-856/S-01
Uloric/Febuxostat tablets 80 mg and 120 mg

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this page is the manifestation of the electronic signature.**

/s/

Tatiana Oussova
7/17/2006 01:22:13 PM
MEDICAL OFFICER

Joel Schiffenbauer
7/17/2006 02:37:45 PM
MEDICAL OFFICER



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CLINICAL REVIEW

From: Joel Schiffenbauer, MD, Team Leader/DAARP

To: NDA 21-856

RE: Febuxostat/complete response

Date: July 3, 2006

Summary:

The sponsor has not satisfactorily addressed the cardiovascular issues associated with the use of febuxostat. However, the sponsor has addressed the issue of co-use of febuxostat with warfarin and the potential for bleeding. Therefore, this NDA should remain approvable.

Background:

Prevalence of self reported gout in the US in 1986 was 13.6 per 1000 men and 6.4 per 1000 women but is increasing in the population and now may exceed 1%. Prevalence among African Americans may be higher than among Caucasian men. It is estimated that in 2004 there were 3-5 million patients with gout in the US and that upwards of 1.6 million are treated with allopurinol (see slides from the June 2, 2004 Arthritis Advisory Committee meeting), and these numbers are also increasing. Therefore, exposure to a new drug such as febuxostat with potentially superior efficacy (at least in regards to lowering serum uric acid), will be considerable.

This document reviews the sponsor's complete response to the approvable letter for NDA 21-856.

NDA review

The following comments are summarized from the original NDA review and provide an overview of the safety concerns raised by review of data presented at the time of the original NDA submission:

There are a number of safety concerns with the use of febuxostat raised by the data presented in this NDA (phase II and III studies). These concerns will be summarized here. For a more complete discussion of safety related issues, the reader is referred to Dr. T. Oussova's safety review.

First, across the entire NDA data base there were eight deaths (please see Table of deaths in Dr. Oussova's review; also sponsor's Table 3.3a in the safety update report[SUR]). All occurred in the febuxostat treatment arm. There were no deaths in the allopurinol comparator arm. There were 2 MIs and 2 cases of respiratory failure with febuxostat. There were also 2 cases of retroperitoneal hemorrhage, both in the febuxostat treatment group (in addition to these 2 deaths due to retroperitoneal hemorrhage there was one SAE, and one increased INR reported as an SAE with febuxostat and none with allopurinol).

Second, across the entire NDA data base there were more cardiovascular thromboembolic events in the febuxostat treatment group compared to either placebo or allopurinol (please see Tables 3.6a, 3.8.2, and 3.12.2.1.3 in the sponsor's safety update report and comparable tables in Dr. Oussova's review including table 11). For example, there were 7 CVA's (based on Dr. Oussova's adjudication of events; the sponsor reported 3 CVA's), 2 TIA's, and 12 MI's in the febuxostat group vs zero CVA/TIA and one MI in the allopurinol group in the randomized controlled studies (009, 010, and 004). In addition, there were 3 DVT/PE's in the febuxostat group vs zero in the allopurinol group. In the (4 month) safety update report the numbers are 21 febuxostat vs 1 allopurinol for the combination endpoint of MI, stroke, TIA, and cardiac arrest.

Furthermore, there are a number of additional concerns. There were 8 cases of CHF in febuxostat vs one in allopurinol (again, in the controlled trials). There were 8 cases of SVT/a-fib in the febuxostat group vs 0 in allopurinol. There were 7 cases of pneumonia with febuxostat vs 0 with allopurinol; there were 4 cases of renal failure with febuxostat vs 0 with allopurinol. Even taking into account the differences in numbers exposed (randomization was usually in a 2:1 ratio between febuxostat and allopurinol and patient-years of exposure approaches 4 fold for febuxostat vs allopurinol), the rates of events in the febuxostat group appear to be greater than in the allopurinol treatment group.

The numbers of discontinuations for skin related events is higher in the febuxostat group: 17 with 2 considered to be severe in intensity with febuxostat vs 2 events, both

considered moderate in intensity, with allopurinol (see Table 3.5d in the original integrated summary of safety [ISS]). However, there were no cases of Stevens-Johnson, toxic epidermal necrolysis, or bullous rash reported in any group.

For liver related discontinuations, there were 28 with 2 severe (9 mild changes) in the febuxostat group vs 5 with zero severe (2 mild and 3 moderate changes) in the allopurinol group (see Table 3.6o in the original ISS; in the SUR there were 4 more cases on febuxostat). Two subjects in the febuxostat group developed ALT greater than or equal to 10X with concurrent total bilirubin greater than or equal to 2 mg/dL as compared to none in the allopurinol group. One of these subjects temporarily discontinued the drug but later resumed dosing and completed the study. There was one case of acute hepatitis (serious adverse event) in the febuxostat group vs 0 in the allopurinol group (there were a total of 4 liver related SAEs on febuxostat vs 1 on allopurinol; see Table 3.6n in the ISS).

In summary, the totality of the safety profile for febuxostat is of concern. The overall mortality rate for febuxostat is higher than for allopurinol, even though there is no single cause of death that appears to stand out. Two cases of retroperitoneal hemorrhage in a data base of this size, is also disturbing (most likely related to changes in INR in patients on warfarin). Furthermore, in the context of the higher rate of CV related SAEs in the febuxostat group, the 2 deaths related to MIs are of greater concern. In addition to CV thromboembolic issues, there is an increase in SVT, and a higher rate of discontinuations due to skin and liver related events, some of which were labeled as severe, in the febuxostat group.

Therefore, based on the above assessments, the risk/benefit analysis is not favorable for this drug at this time. However, it is recommended that an approvable action be taken based on the demonstrated efficacy and because of the need for additional safety information.

Approvable letter

The following are comments excerpted from the Approvable letter for which the sponsor has now provided a complete response:

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to:

1. Further evaluate the safety profile of Uloric, especially in regard to its potential to result in cardiovascular adverse events. Our review of the safety database submitted in your application raises concerns regarding the potential for Uloric to cause clinically

significant cardiovascular/thrombotic adverse events in excess to that seen with allopurinol or placebo, even when exposure-over-time is factored into the analysis. This safety signal may be addressed by providing further comparative controlled clinical safety data or, possibly, through reanalyses of the current database (augmented by any recently completed or on-going studies) that demonstrate the apparent signal of increased risk is not predictive of clinically important differences. Should a differential signal of thromboembolic CV events remain upon the analysis of any new data and/or reanalyses of existing data, we would strongly encourage you to consider proposing the use of lower doses of Uloric, rather than those proposed.

2. Evaluate the potential for concomitant administration of warfarin and Uloric to result in hemorrhagic adverse events, and further address the potential for Uloric to cause hemorrhagic events without co-administration of an anticoagulant . A significant concern exists due to the finding that two subjects died as a result of retroperitoneal hemorrhages while being treated with Uloric, both of whom were receiving warfarin as well. Additional hemorrhagic events were also noted in the safety database. We do not agree with your conclusion that there were no drug-drug interaction with warfarin in the clinical pharmacology study, due to our conclusion that the drug-drug interaction study with warfarin was inadequate to allow for definitive conclusions. The removal of subjects with an increased INR from the final analysis in the warfarin drug-drug interaction trial was problematic. In addition, there were reports of increased INR values in the clinical database in subjects receiving concomitant treatment with Uloric and warfarin.

Data Analysis

The remainder of this review will first focus on the sponsor's response to the cardiovascular issues and then on the clinical aspects of the potential for warfarin interaction with febuxostat. The reader is referred to the OCPB review for comments regarding the warfarin interaction study.

A. Cardiovascular analysis

The sponsor disputes the finding of a CV signal. In order to address this issue, the sponsor had the original data adjudicated by a blinded cardiologist and presents these analyses, as well as updated safety data collected since the previous submission in support of their interpretation.

The data will first be presented for APTC events corresponding to investigator reported events for the controlled clinical trials (as originally presented in the NDA), followed by the results from the open label extension portion of these trials. Subsequently, the data will be presented for APTC events corresponding to the adjudicated analyses for the same controlled trials and open label extensions.

Table 1 below, describes the Meddra terms used to generate the subsequent tables. Primary APTC events focus on CV deaths, and non-fatal MIs and strokes.

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Table 1: APTC Criteria and Corresponding MedDRA Preferred Terms in the TAP Database for the Investigator-Reported Analyses

| APTC Criterion | MedDRA Preferred Term | Category |
|---|--|--|
| Cardiovascular death | The following MedDRA PTs were associated with cardiovascular death: Acute myocardial infarction Cardiac arrest Cardiac failure congestive Myocardial infarction Retroperitoneal haemorrhage | These events are summarized as primary APTC events in this document |
| Non-fatal myocardial infarction | Acute myocardial infarction ^a Myocardial infarction ^a Silent myocardial infarction ^a | |
| Non-fatal stroke | Brain stem infarction ^a Cerebrovascular accident ^a Lacunar infarction ^a Cerebral haemorrhage ^a | |
| Non-fatal cardiac arrest | Cardiac arrest ^a | |
| Angina | Acute coronary syndrome Angina pectoris Angina unstable | These events are summarized as secondary APTC events in this document |
| Revascularization | Coronary artery atherosclerosis ^b Coronary artery disease ^b Coronary artery occlusion ^b Coronary artery stenosis ^b | |
| Transient ischemic attack | Transient ischaemic attack | |
| Venous and peripheral arterial vascular thrombotic events | Pulmonary embolism Deep vein thrombosis Thrombosis Ischaemia | |
| Non-fatal congestive heart failure | Cardiac failure congestive ^b | |

a Only non-fatal events

b Approximately 85% of the reported events also had documentation of revascularization

Cross-reference: Statistical Table 3.14

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Table 2: Incidence Rates and Confidence Intervals for Subjects with Investigator-Reported Treatment-Emergent Primary APTC Events in the Phase 3 Randomized Controlled Studies

| Primary APTC | Treatment Group, n (RPY) | | | | | |
|---------------------------------|--------------------------|--------------------|-------------------|-------------------|------------------|-------------------|
| | Placebo | Febuxostat | | | | Allopurinol |
| | | Total | 80 mg QD | 120 mg QD | 240 mg QD | |
| Events | N=134 PY=59.9 | N=1177 PY=671.1 | N=523 PY=312.6 | N=520 PY=304.5 | N=134 PY=54.0 | N=521 PY=333.7 |
| Overall | 0 | 9 (1.34) | 4 (1.28) | 5 (1.64) | 0 | 1 (0.3) |
| 95% CI ^a | (0.00-6.16) | (0.61-2.55) | (0.35-3.28) | (0.53-3.83) | (0.00-6.83) | (0.008-1.67) |
| CV death | 0 | 3 (0.45) | 2 (0.64) | 1 (0.33) | 0 | 0 |
| 95% CI ^a | (0.00-6.16) | (0.09-1.31) | (0.08-2.31) | (0.008-1.83) | (0.00-6.83) | (0.00-1.11) |
| Non-fatal myocardial infarction | 0 | 5 (0.75) | 2 (0.64) | 3 (0.99) | 0 | 1 (0.3) |
| 95% CI ^a | (0.00-6.16) | (0.24-1.74) | (0.08-2.31) | (0.20-2.88) | (0.00-6.83) | (0.008-1.67) |
| Non-fatal stroke | 0 | 1 (0.15) | 0 | 1 (0.33) | 0 | 0 |
| 95% CI ^a | (0.00-6.16) | (0.004-0.83) | (0.00-1.18) | (0.008-1.83) | (0.00-6.83) | (0.00-1.11) |
| Non-fatal cardiac arrest | 0 | 1 (0.15) | 0 | 1 (0.33) | 0 | 0 |
| 95% CI ^a | (0.00-6.16) | (0.004-0.83) | (0.00-1.18) | (0.008-1.83) | (0.00-6.83) | (0.00-1.11) |

Studies included: C02-009 and C02-010

RPY = rate per 100 patient-years of exposure

Adverse events summarized were reported after the first dose of study drug and within 30 days of the last dose of study drug.

a CI calculated based on Poisson distribution

Cross-reference: Statistical Table 3.17.2.2 (Safety Update, February 2006)

(Of note, numbers of “overall” indicate number of patients while numbers under each event indicate the number of actual events; therefore one patient may have more than one event and numbers may not add up in each column. For example, under the “Total” column, for “Overall” there are 9 while the number of events such as CV death, non-fatal MI etc, add up to 10)

As can be seen from this table, the percent of patients with a primary APTC event in the febuxostat group is 0.8 vs 0.2 in the allopurinol group (4 fold excess), and all of the deaths (albeit only 3) are in the febuxostat group. The rates per 100 patient years of exposure for *overall events* are 1.34 for febuxostat vs 0.3 for allopurinol (again a 4 plus fold excess).

Table 3: Incidence Rates and Confidence Intervals for Subjects with Treatment-Emergent Primary and Secondary Investigator-Reported APTC Events in the Phase 3 Randomized Controlled Studies

| Primary and Secondary APTC Events | Treatment Group, n (%) | | | | | |
|---|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|---|
| | Placebo (N=134) | Febuxostat | | | | Allopurinol 300/100 mg QD (N=521) |
| | | Total (N=1177) | 80 mg QD (N=523) | 120 mg QD (N=520) | 240 mg QD (N=134) | |
| Overall 95% CI ^a | 1 (0.7) (0.019-4.09) | 25 (2.1) (1.38-3.12) | 13 (2.5) (1.33-4.21) | 11 (2.1) (1.06-3.75) | 1 (0.7) (0.019-4.09) | 7 (1.3) (0.54-2.75) |
| CV death | 0 | 3 (0.3) | 2 (0.4) | 1 (0.2) | 0 | 0 |
| Non-fatal myocardial infarction | 0 | 5 (0.4) | 2 (0.4) | 3 (0.6) | 0 | 1 (0.2) |
| Non-fatal stroke | 0 | 1 (<0.1) | 0 | 1 (0.2) | 0 | 0 |
| Non-fatal cardiac arrest | 0 | 1 (<0.1) | 0 | 1 (0.2) | 0 | 0 |
| Angina | 0 | 6 (0.5) | 4 (0.8) | 1 (0.2) | 1 (0.7) | 2 (0.4) |
| Revascularization | 1 (0.7) | 6 (0.5) | 4 (0.8) | 2 (0.4) | 0 | 4 (0.8) |
| Transient Ischemic Attack | 0 | 2 (0.2) | 2 (0.4) | 0 | 0 | 0 |
| Venous and peripheral arterial vascular thrombotic events | 0 | 2 (0.2) | 0 | 2 (0.4) | 0 | 0 |
| Non-fatal congestive heart failure | 0 | 3 (0.3) | 2 (0.4) | 1 (0.2) | 0 | 1 (0.2) |

Studies included: C02-009 and C02-010

^a CI calculated based on binomial distribution

Cross-reference: Statistical Table 3.16.4.1 and 3.17.2.3

For primary and secondary APTC events, the excess of events in the febuxostat group is reduced (2.1 vs 1.3%) although it is still trending against febuxostat. Concerns with the use of secondary APTC events are that: 1) the severity of events such as angina is less than an MI or stroke, and 2) the diagnosis is likely to be more suspect than the “hard” endpoints of MI or stroke. By way of comparison, for the analyses of CV events with the Cox-2 inhibitors, the analyses of primary APTC events appeared to be much more consistent between the various Cox-2 inhibitors, and was therefore the preferred analysis.

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Table 4: Incidence of Investigator-Reported Treatment-Emergent Primary APTC Events per 100 Patient-Years of Exposure in the Long-Term Extension Studies

| | Treatment Group | | | | |
|---------------------------------|------------------------------|-----------------------------|--------------------------------|--------------------------------|------------------------------------|
| | Febuxostat | | | | Allopurinol |
| | Total N=1143 PY=1933.7 | 40 mg QD N=12 PY=33.0 | 80 mg QD N=910 PY=1265.4 | 120 mg QD N=522 PY=635.3 | 300/100 mg QD N=178 PY=133.3 |
| Primary APTC Events | n (RPY) | n (RPY) | n (RPY) | n (RPY) | n (RPY) |
| Overall | 28 (1.4) | 1 (3.0) | 18 (1.4) | 9 (1.4) | 1 (0.8) |
| 95% CI ^a | (0.96-2.09) | (0.077-16.89) | (0.84-2.25) | (0.648-2.69) | (0.019-4.18) |
| CV death | 4 (0.2) | 0 | 1 (<0.1) | 3 (0.5) | 0 |
| 95% CI ^a | (0.056-0.53) | (0-11.2) | (0.002-0.44) | (0.097-1.38) | (0-2.77) |
| Non-fatal myocardial infarction | 15 (0.8) | 0 | 12 (0.9) | 3 (0.5) | 1 (0.8) |
| 95% CI ^a | (0.43-1.28) | (0-11.2) | (0.490-1.66) | (0.097-1.38) | (0.019-4.18) |
| Non-fatal stroke | 9 (0.5) | 1 (3.0) | 5 (0.4) | 3 (0.5) | 0 |
| 95% CI ^a | (0.21-0.884) | (0.077-16.9) | (0.128-0.922) | (0.097-1.38) | (0-2.77) |

N = number of subjects dosed; PY = Patient year; RPY = rate per 100 patient-years of exposure

Studies included: C02-021 and TMX-01-005

Adverse events summarized were reported after the first dose of study drug and within 30 days of the last dose of study drug. Death events after 30 days of the last dose of study drug were also included. Subjects with one or more adverse events within a category are counted only once in that category.

a 95% CI were calculated based on Poisson distribution

Cross-reference: Statistical Table 3.16.1.2 and 3.17.1.2

The extension studies again show a trend against febuxostat (1.4 vs 0.8) for overall events. A problem with the extension studies is the potential for depletion of susceptibles, that is patients with a high risk for either MI/stroke or death have dropped out and so are no longer available to have an event. An additional difficulty with analyzing the long term extension data is the imbalance between exposure to allopurinol vs febuxostat. There is considerably more exposure data for the febuxostat group than the allopurinol group.

Adding all cases from phase 3 trials and extension studies and estimating the patient years of exposure for the entire population and dosing period, the following is determined:

In total, there are approximately 2605 patient years of exposure for febuxostat vs 467 patient years of exposure for allopurinol. There are a total of 37 cases of APTC events for febuxostat vs 2 cases for allopurinol (derived by adding the cases in tables 2 and 4). Even taking into account the 5.5 fold excess exposure for febuxostat (multiplying 2 allopurinol

cases by 5.5 gives a corrected estimate of 11 cases in the allopurinol group) there are approximately 3.3 fold the number of cases in the febuxostat treatment group vs allopurinol (37 vs 11).

A Kaplan-Meier analysis (not shown) reveals that events are occurring through out the exposure period and are not occurring particularly early or late during this period.

Table 5: Incidence of Investigator-Reported Primary and Secondary APTC Events per 100 Patient-Years of Exposure in the Long-Term Extension Studies

| Primary and Secondary APTC Events | Treatment Group | | | | |
|---|------------------------------|-----------------------------|--------------------------------|--------------------------------|------------------------------------|
| | Febuxostat | | | | Allopurinol |
| | Total N=1143 PY=1933.7 | 40 mg QD N=12 PY=33.0 | 80 mg QD N=910 PY=1265.4 | 120 mg QD N=522 PY=635.3 | 300/100 mg QD N=178 PY=133.3 |
| | n (RPY) | n (RPY) | n (RPY) | n (RPY) | n (RPY) |
| Overall | 58 (3.0) | 1 (3.0) | 37 (2.9) | 21 (3.3) | 4 (3.0) |
| 95% CI ^a | (2.28-3.88) | (0.077-16.89) | (2.06-4.03) | (2.05-5.05) | (0.817-7.68) |
| CV death | 4 (0.2) | 0 | 1 (<0.1) | 3 (0.5) | 0 |
| Non-fatal myocardial infarction | 15 (0.8) | 0 | 12 (0.9) | 3 (0.5) | 1 (0.8) |
| Non-fatal stroke | 9 (0.5) | 1 (3.0) | 5 (0.4) | 3 (0.5) | 0 |
| Angina | 10 (0.5) | 0 | 7 (0.6) | 4 (0.6) | 0 |
| Revascularization | 12 (0.6) | 0 | 9 (0.7) | 3 (0.5) | 1 (0.8) |
| Transient Ischemic Attack | 2 (0.1) | 0 | 0 | 2 (0.3) | 0 |
| Venous and peripheral arterial vascular thrombotic events | 6 (0.3) | 0 | 6 (0.5) | 0 | 1 (0.8) |
| Non-fatal congestive heart failure | 9 (0.5) | 0 | 5 (0.4) | 4 (0.6) | 1 (0.8) |

N = number of subjects dosed; PY = Patient year; RPY = rate per 100 patient-years of exposure

Studies included: C02-021 and TMX-01-005

Adverse events summarized were reported after the first dose of study drug and within 30 days of the last dose of study drug. Death events after 30 days of the last dose of study drug were also included. Subjects with one or more adverse events within a category are counted only once in that category.

^a 95% CI were calculated based on Poisson distribution

Cross-reference: Statistical Table 3.16.2.2 and 3.17.1.4

Primary and secondary events in the long term extension trials reveals little difference between the treatment groups.

Adjudicated events

In response to the approvable letter, the sponsor submitted a blinded re-adjudication of the cases. Although the adjudication was performed by a third party in a blinded fashion, it was a post-hoc analysis with the potential for introduction of bias in the sponsors favor. Knowing that almost all of the cases of CV events occurred in the febuxostat treatment group, it is possible to conclude that any re-adjudication of APTC events to non-APTC events, might eventually favor the sponsor by reducing the rate of events in the febuxostat group and thereby reducing the ratio of events compared to allopurinol. Although the following section presents these analyses, this reviewer believes that the

original investigator reported events should remain as the primary analysis. Furthermore, our cardio-renal group also performed a blinded adjudication of events. In their consult they comment that in cases where adjudication is not possible, investigator reported events should be the preferred analysis (see section below, *Cardio-renal re-adjudication of events*). Future trials should establish definitions and rules for which events will be adjudicated, and establish an independent adjudication committee to review each case.

There are approximately 8 cases (see cardiologists listing of cases with comments) with either “insufficient information” or “no other data”, which makes a specific diagnosis difficult. If even a subset of these events were adjudicated as APTC events, this would add additional cases to the number of events for febuxostat. In any future trial, every effort to collect all the appropriate and necessary data will be crucial, to reduce the number of these types of cases.

Table 6: Percentages of Subjects with Treatment-Emergent Adjudicated APTC Events in the Phase 3 Randomized Controlled Studies

| | Treatment Group | | | | | |
|---------------------|--------------------|-------------------|---------------------|----------------------|----------------------|---|
| | Placebo (N=134) | Febuxostat | | | | Allopurinol 300/100 mg QD (N=521) |
| | | Total (N=1177) | 80 mg QD (N=523) | 120 mg QD (N=520) | 240 mg QD (N=134) | |
| APTC Events | | | | | | |
| Number of Subjects | 0 | 7 | 4 | 3 | 0 | 1 |
| Rate (%) | 0 | 0.59 | 0.76 | 0.58 | 0 | 0.19 |
| 95% CI ^a | (0.00-2.71) | (0.239-1.22) | (0.209-1.95) | (0.119-1.68) | (0.00-2.71) | (0.005-1.07) |
| CV Death | | | | | | |
| Number of Subjects | 0 | 3 | 2 | 1 | 0 | 0 |
| Rate (%) | 0 | 0.25 | 0.38 | 0.19 | 0 | 0 |
| 95% CI ^a | (0.00-2.71) | (0.053-0.743) | (0.046-1.37) | (0.005-1.07) | (0.00-2.71) | (0.00-0.706) |
| Non-fatal MI | | | | | | |
| Number of Subjects | 0 | 4 | 2 | 2 | 0 | 1 |
| Rate (%) | 0 | 0.34 | 0.38 | 0.38 | 0 | 0.19 |
| 95% CI ^a | (0.00-2.71) | (0.093-0.868) | (0.046-1.37) | (0.047-1.38) | (0.00-2.71) | (0.005-1.07) |

Studies included: C02-009 and C02-010

a The confidence intervals are calculated based on binomial distribution

Cross-reference: Statistical Table 3.19.2.1

Even taking into account the re-adjudication of cases and taking into account differences in exposure, there is still a 3 fold excess of CV events in the febuxostat treatment group compared to allopurinol. Note also that compared to table 1 there is a decrease in 2 cases in the febuxostat group after adjudication.

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Table 7: Incidences of Treatment-Emergent Adjudicated APTC Events Per 100 Patient-Years of Exposure in the Long-Term Extension Studies

| | Treatment Group | | | | |
|-------------------------|----------------------------------|---------------------------------|------------------------------------|------------------------------------|---|
| | Febuxostat | | | | Allopurinol 300/100 mg QD (N=178) (PY=133.3) |
| | Total (N=1143) (PY=1933.7) | 40 mg QD (N=12) (PY=33.0) | 80 mg QD (N=910) (PY=1265.4) | 120 mg QD (N=522) (PY=635.3) | |
| APTC Events | | | | | |
| Number of Subjects | 21 | 1 | 12 | 8 | 1 |
| Rate per 100 PY | 1.09 | 3.03 | 0.95 | 1.26 | 0.75 |
| 95% CI ^a | (0.672-1.66) | (0.077-16.9) | (0.490-1.65) | (0.544-2.48) | (0.019-4.18) |
| CV Death | | | | | |
| Number of Subjects | 4 | 0 | 1 | 3 | 0 |
| Rate per 100 PY | 0.21 | 0 | 0.08 | 0.47 | 0 |
| 95% CI ^a | (0.056-0.530) | (0-11.2) | (0.002-0.440) | (0.097-1.38) | (0-2.77) |
| Non-fatal MI | | | | | |
| Number of Subjects | 9 | 0 | 7 | 2 | 1 |
| Rate per 100 PY | 0.47 | 0 | 0.55 | 0.31 | 0.75 |
| 95% CI ^a | (0.213-0.884) | (0-11.2) | (0.222-1.14) | (0.038-1.14) | (0.019-4.18) |
| Non-fatal Stroke | | | | | |
| Number of Subjects | 8 | 1 | 4 | 3 | 0 |
| Rate per 100 PY | 0.41 | 3.03 | 0.32 | 0.47 | 0 |
| 95% CI ^a | (0.179-0.815) | (0.077-16.9) | (0.086-0.809) | (0.097-1.38) | (0-2.77) |

Studies included: TMX-01-005 and C02-021

a The confidence intervals are calculated based on Poisson distribution

Cross-reference: Statistical Table 3.19.1.2

In the extension studies, the rate of CV events is more similar between the treatment groups although there is still a slight excess of events in the febuxostat group (1.09 vs 0.75). Of note, with re-adjudication the number of events in the febuxostat group has again decreased (by 7 events; compare to table 4). In the context of a small number of events, this re-adjudication process has led to an alteration in the ratio of events.

Combining the adjudicated cases from the phase 3 trials and extension studies provides the following numbers: 28 cases in febuxostat vs 2 cases in allopurinol. Multiplying the 2 cases by 5.5 (to compensate for the differences in exposure) gives us 11 cases in allopurinol, and compared to 28 cases seen with febuxostat, still gives a 2.8 fold excess of cases in the febuxostat treatment group.

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Table 8: Treatment-Emergent Cardiovascular Deaths in Combined Phase 3 Randomized Controlled and Long-Term Extension Studies

| | Placebo (N=134) (PY=59.9) | Treatment Febuxostat | | | | | Allopurinol 300/100 (N=642) (PY=467.1) |
|---------------------|---------------------------------|----------------------------------|------------------------------|--------------------------------|---------------------------------|--------------------------------|---|
| | | Total (N=1692) (PY=2604.8) | 40 mg (N=12) (PY=33.0) | 80 mg (N=1221) (PY=1578) | 120 mg (N=909) (PY=939.8) | 240 mg (N=134) (PY=54.0) | |
| Number of CV Deaths | 0 | 7 | 0 | 3 | 4 | 0 | 0 |
| Per 100 PY | 0 | 0.27 | 0 | 0.19 | 0.43 | 0 | 0 |
| 95%CI | (0-6.16) | (0.108-0.554) | (0-11.2) | (0.039-0.556) | (0.116-1.09) | (0-6.83) | (0-0.79) |

Studies included: TMX-01-005, C02-009, C02-010, and C02-021

Cross-reference: Statistical Table 3.13.3

A safety update including new data up to February 2006 reveals 2 additional cases of APTC events (deaths) attributed to febuxostat. Therefore the total number of APTC events (deaths) is 9 febuxostat vs 0 allopurinol. It is important to emphasize that all of the CV related mortality occurred in the febuxostat treatment group. During the controlled trials which lasted a maximum of one year, there were a total of 3 deaths (in 1692 patients) for a rate of one death per 564 treated patients per year. In total there were nine deaths out of 1692 total febuxostat treated patients giving us an estimate of one death per 188 treated patients over the entire length of the study.

Cardio-renal re-adjudication of events

Thirteen cases of interest were sent blinded to the cardio-renal division to obtain independent adjudication of events. These cases were ones that the sponsor's cardiologist had re-adjudicated and which led to a change in the diagnosis based on his expert opinion. Therefore, the following consult was sent to the Cardio-renal Division:

We have received an analysis of cardiovascular events in the febuxostat development program (treatment of hyperuricemia). Please adjudicate the following 13 cases that are being sent to you blinded and hard copy (case numbers: 4730; 2790; 2019; 2403; 2587; 4479; 2223; 4959; 4186; 310; 4963; 5000; 4665), as to whether they meet the definition of primary (or secondary) APTC events. We request that this be a blinded analysis (the drug name has been blacked out). These cases have been reviewed by the sponsor's outside cardiologist and we wish to evaluate the appropriateness of the diagnoses.

The following response was received:

The cardio-renal consultant felt that 7 cases had insufficient information to apply criteria or otherwise confirm the event. Therefore, they concluded that adjudication was largely an exercise in futility and in such a case the investigators diagnosis was accepted. For example, for case #2223 the sponsor consultant re-adjudicated the case from an APTC event to a non-APTC event. The cardio-renal group did not agree. This was also true for case #2790 (re-adjudicated from APTC to non-APTC event).

We can conclude that without pre-defined endpoints and rigorous collection of data, post hoc adjudication is problematic.

B. Warfarin interaction

The clinical consequences of the use of warfarin in patients on febuxostat is difficult to interpret from the data presented. The initial NDA presented data on 2 patients who died with retroperitoneal hemorrhage. The first patient had a CT report that did not support a diagnosis of retroperitoneal hemorrhage, but did not rule out blood in the abdomen. The second patient likely did have a retroperitoneal hemorrhage but it is not clear if she was actually receiving febuxostat during her hospitalization. In the phase 3 trials one patient on febuxostat developed retroperitoneal hemorrhage (previously mentioned) and one patient on allopurinol developed epistaxis. During the long term extension studies 2 patients on 80 mg febuxostat, one patient on febuxostat 120 mg and no patients on allopurinol developed at least one bleeding adverse event while on warfarin. For patients on warfarin before entering a trial, 3 patients had an increased PT on febuxostat 120 mg (25%) and one on febuxostat 80 mg (9%) had an increased PT. vs one on allopurinol (11%). There are too few events to make any firm conclusions from the clinical data.

The following tables summarize these data.

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Table 9: Number (%) of Subjects with Bleeding Adverse Events in the Phase 3 Randomized Controlled Studies

| All Subjects in Phase 3 Randomized Controlled Studies, n (%) | | | | | | |
|---|-----------------|----------------|------------------|-------------------|-------------------|-----------------------------------|
| Bleeding Adverse Events | Placebo (N=134) | Febuxostat | | | | Allopurinol 300/100 mg QD (N=521) |
| | | Total (N=1177) | 80 mg QD (N=523) | 120 mg QD (N=520) | 240 mg QD (N=134) | |
| All Events | 4 (3.0) | 55 (4.7) | 26 (5.0) | 23 (4.4) | 6 (4.5) | 21 (4.0) |
| Treatment-related Events | 1 (0.7) | 5 (0.4) | 3 (0.6) | 1 (0.2) | 1 (0.7) | 3 (0.6) |
| While Subjects were Taking Anticoagulants or Antithrombotic Agents, n (%) | | | | | | |
| Bleeding Adverse Events ^a | Placebo (N=40) | Total (N=298) | 80 mg QD (N=130) | 120 mg QD (N=125) | 240 mg QD (N=43) | 300/100 mg QD (N=107) |
| | | | | | | |
| Treatment-related Events | 0 | 2 (0.7) | 1 (0.8) | 1 (0.8) | 0 | 2 (1.9) |
| While Subjects were Taking Warfarin, n (%) | | | | | | |
| Bleeding Adverse Events ^b | Placebo (N=7) | Total (N=32) | 80 mg QD (N=15) | 120 mg QD (N=15) | 240 mg QD (N=2) | 300/100 mg QD (N=12) |
| | | | | | | |
| Treatment-related Events | 0 | 0 | 0 | 0 | 0 | 1 (8.3) |
| While Subjects were Taking Heparin, n (%) | | | | | | |
| Bleeding Adverse Events ^c | Placebo (N=0) | Total (N=12) | 80 mg QD (N=6) | 120 mg QD (N=6) | 240 mg QD (N=0) | 300/100 mg QD (N=2) |
| | | | | | | |
| Treatment-related Events | -- | 0 | 0 | 0 | -- | 0 |

Studies included: C02-009 and C02-010

a Includes events that occurred within 7 days after taking warfarin, 2 days after taking heparin, and 1 day after taking other anticoagulants or antithrombotic agents.

b Includes events that occurred within 7 days after taking warfarin.

c Includes events that occurred within 2 days after taking heparin.

Cross-references: Statistical Tables 3.11.10.1, 3.11.10.2, 3.11.10.3, 3.11.10.4, 3.12.10.1, 3.12.10.2, 3.12.10.3 and 3.12.10.4

Specifically, there is no excess of events comparing allopurinol and febuxostat, in patients on warfarin. If anything, there is a slight increase in events in patients on allopurinol with warfarin. In the warfarin label, allopurinol is noted to potentially lead to an increased INR.

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Table 10: Bleeding Adverse Events Reported by >1 Subject in Any Treatment Group in Phase 3 Randomized Controlled Studies

| MedDRA High Level Term MedDRA Preferred Term | Placebo (N=134) n (%) | Febuxostat | | | | Allopurinol 300/100 mg QD (N=521) n (%) |
|--|-----------------------------|----------------------------|------------------------------|-------------------------------|-------------------------------|--|
| | | Total (N=1177) n (%) | 80 mg QD (N=523) n (%) | 120 mg QD (N=520) n (%) | 240 mg QD (N=134) n (%) | |
| Total Subjects with ≥1 event | 4 (3.0) | 55 (4.7) | 26 (5.0) | 23 (4.4) | 6 (4.5) | 21 (4.0) |
| Intestinal Haemorrhages | 0 | 6 (0.5) | 1 (0.2) | 3 (0.6) | 2 (1.5) | 3 (0.6) |
| Rectal Haemorrhage | | | | | | |
| Non-Site Specific | | | | | | |
| Gastrointestinal Haemorrhages | 1 (0.7) | 5 (0.4) | 4 (0.8) | 0 | 1 (0.7) | 3 (0.6) |
| Gastrointestinal Haemorrhage, Haematemesis, Haematochezia | | | | | | |
| Chest and Lung Injuries NEC | 0 | 1 (<0.1) | 1 (0.2) | 0 | 0 | 0 |
| Haemothorax | | | | | | |
| Skin Injuries NEC | 1 (0.7) | 14 (1.2) | 4 (0.8) | 8 (1.5) | 2 (1.5) | 7 (1.3) |
| Contusion | | | | | | |
| Urinary Abnormalities | 1 (0.7) | 11 (0.9) | 6 (1.1) | 4 (0.8) | 1 (0.7) | 1 (0.2) |
| Haematuria | | | | | | |
| Nasal Disorders NEC | 0 | 4 (0.3) | 2 (0.4) | 2 (0.4) | 0 | 5 (1.0) |
| Epistaxis | | | | | | |
| Purpura and Related Conditions | 0 | 6 (0.5) | 2 (0.4) | 3 (0.6) | 1 (0.7) | 1 (0.2) |
| Ecchymosis, Increased Tendency to Bruise, Petechiae | | | | | | |
| Haemorrhages NEC | 0 | 3 (0.3) | 2 (0.4) | 1 (0.2) | 0 | 0 |
| Haematoma | | | | | | |

NEC = not elsewhere classified

Cross-reference: Statistical Table 3.11.10.1

It is not clear why there should be a greater incidence of hematuria on febuxostat than on allopurinol. The rate of purpura etc is similar between febuxostat and allopurinol and higher than placebo, but the number of events is small. Other events are similar in occurrence between allopurinol and febuxostat.

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Table 11: Overall Incidence Rates of Bleeding Adverse Events per 100 Patient-Years of Exposure in Long-Term Extension Studies

| All Subjects in Long-Term Extension Studies | | | | | |
|--|----------------------------------|---------------------------------|------------------------------------|------------------------------------|--|
| Bleeding Adverse Events | Febuxostat | | | | Allopurinol |
| | Total (N=1143) (PY=1933.7) | 40 mg QD (N=12) (PY=33.0) | 80 mg QD (N=910) (PY=1265.4) | 120 mg QD (N=522) (PY=635.3) | 300/100 mg QD (N=178) (PY=133.3) |
| All Events | 3.6 | 0 | 3.6 | 3.9 | 2.3 |
| Treatment-related Events | 0.5 | 0 | 0.2 | 0.9 | 0 |
| While Subjects were Taking Anticoagulants or Antithrombotic Agents | | | | | |
| Bleeding Adverse Events ^a | Total (N=314) (PY=568.7) | 40 mg QD (N=1) (PY=4.2) | 80 mg QD (N=251) (PY=407.8) | 120 mg QD (N=119) (PY=150.6) | 300/100 mg QD (N=43) (PY=34.6) |
| | All Events | 3.9 | 0 | 4.2 | 3.3 |
| Treatment-related Events | 0.5 | 0 | 0 | 2.0 | 0 |
| While Subjects were Taking Warfarin | | | | | |
| Bleeding Adverse Events ^c | Total (N=41) (PY=76.7) | 40 mg QD (N=0) -- | 80 mg QD (N=27) (PY=47.6) | 120 mg QD (N=19) (PY=28.2) | 300/100 mg QD (N=8) (PY=6.9) |
| | All Events | 3.9 | -- | 4.2 | 3.6 ^b |
| Treatment-related Events | 1.3 ^b | -- | 0 | 3.6 ^b | 0 |
| While Subjects were Taking Heparin | | | | | |
| Bleeding Adverse Events ^d | Total (N=30) (PY=48.1) | 40 mg QD (N=0) -- | 80 mg QD (N=20) (PY=31.6) | 120 mg QD (N=11) (PY=14.7) | 300/100 mg QD (N=3) (PY=3.7) |
| | All Events | 2.1 ^b | -- | 0 | 6.8 ^b |
| Treatment-related Events | 2.1 ^b | -- | 0 | 6.8 ^b | 0 |

Studies included: TMX-01-005 and C02-021

a Includes events that occurred within 7 days after taking warfarin, 2 days after taking heparin, and 1 day after taking other anticoagulants or antithrombotic agents.

b This represents 1 subject (Subject 4756) who started warfarin and heparin for treatment of lacunar infarction the day of the event.

c Includes events that occurred within 7 days after taking warfarin.

d Includes events that occurred within 2 days after taking heparin.

Cross-references: Statistical Tables 3.9.10.5, 3.9.10.6, 3.9.10.7, 3.9.10.8, 3.10.10.5, 3.10.10.6, 3.10.10.7, and 3.10.10.8

In long term studies, there are no cases of bleeding events while subjects were taking warfarin and allopurinol, although there are events on febuxostat. However, due to the greater number of patients on febuxostat, firm conclusions cannot be drawn.

Table 12: Effects on PT and Warfarin Dosing After Starting Study Drug During Phase 3 Randomized Controlled Clinical Trials

| PT and Warfarin Pattern after Starting Study Drug | Placebo (N=5) | Febuxostat 80 mg (N=11) | Febuxostat 120 mg (N=12) | Febuxostat 240 mg (N=1) | Allopurinol 300/100 mg (N=9) |
|---|---------------|-------------------------|--------------------------|-------------------------|------------------------------|
| Stable warfarin dose and stable PT ^a | 5 | 5 | 8 | 0 | 6 |
| Stable warfarin dose and increased PT | 0 | 1 | 3 ^d | 0 | 1 |
| Stable warfarin dose and decreased PT | 0 | 1 | 0 | 0 | 1 |
| No informative PT ^b | 0 | 3 | 0 | 0 | 1 |
| Change in warfarin dose ^c | 0 | 1 increased dose | 1 increased dose | 1 decreased dose | 0 |

a Stable was defined as no change in warfarin dose and first treatment PT within 3 seconds of range of closest 2 PT values prior to study drug start.

b No informative PT: when there was no change in warfarin dose but no PT measurement predose, or during treatment, or within 2 weeks of end of treatment.

c Change in warfarin dose before the first treatment PT measurement.

d One subject had elevated INR rather than PT

Cross-reference: Appendix 13.4

Three cases of elevated PT occurred on febuoxstat at 120 mg (25% [3/12]) vs one case on allopurinol (11% [1/11]). There may be a dose response (9% at 80 mg vs 25 % at 120 mg).

In addition, there were 6 cases of increased INR on febuxostat discussed in the submission. In 2 of those cases (subject 2368; subject 4551), patients were previously on doses of warfarin and febuxostat was added. Therefore, the increased INR may be related to the addition of febuxostat. One subject had a GI bleed, but in the other subject there was no clinical event. The other cases were either confounded by multiple medications and/or multiple medical problems, or warfarin was started after febuxostat and the interaction if any between the 2 drugs is not clear.

The limited clinical data suggests there may be some interaction between warfarin and febuxostat, although there are too few clinical events to make firm conclusions. Although there was some concern raised during the initial review cycle in regards to the interpretability of the warfarin interaction study (see OCPB review), the data presented does not indicate that an interaction is likely.

Discussion:

Based on a re-analysis of the submitted CV data, a CV signal with the use of febuxostat appears to be present. Various analyses including investigator reported as well as adjudicated CV events demonstrate a signal for CV thrombotic events, including fatal and non-fatal MI, stroke, and sudden death. For investigator reported events there appears to be a 4 fold excess of events in the febuxostat treatment group compared to allopurinol, while for adjudicated events there is at least a 3 fold excess of events. However, post hoc adjudication of events is fraught with difficulties as confirmed by the cardio-renal evaluation of a selected set of events. Never the less, in each analysis, this excess is present, even taking into account the imbalance of exposure to each drug. Just examining the 2 phase 3 controlled trial data, there is still a 3-4 fold excess of events (albeit the number of events is smaller than when the extension studies are included) comparing febuxostat to allopurinol. Unfortunately because of the imbalanced randomization, there is not enough exposure to placebo treatment to allow meaningful comparisons to this treatment group.

To put this data into some perspective; for the VIGOR trial comparing rofecoxib to naproxen, there was a 5 fold excess of CV events in the rofecoxib treatment group. In comparison, for celecoxib in the APC trial (adenoma prevention) the hazard ratio was 3.4 and 2.3 for CV events comparing celecoxib 400 mg and 200 mg respectively, to placebo. In the APPROVE trial (adenoma prevention trial) the hazard ratio was 4.6 for rofecoxib compared to placebo. In observational studies an increased risk of CV events for rofecoxib 50 mg of approximately 2-3 fold was observed, most often compared to non-selective NSAID.

There are a number of additional considerations. If there are \rightarrow allopurinol users with gout in the US, and if we consider that eventually most of these individuals (worst case scenario) will be shifted to febuxostat (or new cases will be started on febuxostat; this is anticipated because of the potential superior efficacy of febuxostat, at least in terms of lowering of serum uric acid), there could potentially be 7000 additional cardiovascular deaths in a year from febuxostat use compared to allopurinol use (derived by dividing $\frac{\text{number of patients on allopurinol in the general population who may eventually take febuxostat}}{2.25 \times 10^2}$ - the number of deaths per patient years of exposure in the controlled studies). This number does not include MIs and strokes. To put these numbers into further perspective, the Tysabri data (for the treatment of multiple sclerosis) identified the development of one case of PML in 1000 patients.

Although not part of the complete response, a further comment about the efficacy of the drug is in order here. The 2 phase 3 trials demonstrate that febuxostat is superior to allopurinol in reducing the level of serum uric acid (but these trials were unable to convincingly demonstrate a reduction in gout flares or size of tophi). Based on this, it is likely that once approved, febuxostat would rapidly replace allopurinol as the preferred treatment for gout and hyperuricemia. However, it remains possible that if allopurinol was used at doses higher than the 300 mg dose used in these trials, the difference between allopurinol and febuxostat efficacy would not be as great. Indeed, it appears

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from PK/PD analyses that doses of febuxostat such as 40 mg would provide the same efficacy as 300 mg allopurinol. Therefore, although the 2 studies support the efficacy of febuxostat and its superiority to allopurinol, the sponsor has apparently chosen doses of febuxostat in order to demonstrate this greater efficacy. The Division recommended that the sponsor consider studying doses less than the 80 and 120 mg doses proposed for marketing. However, to date, the sponsor has not followed this recommendation. It seems possible that lower doses would lead to an overall improved safety profile more similar to allopurinol, but the sponsor would lose the advantage of superior efficacy, which is what they appear to be intent on showing.

The above discussion of CV events must also be considered in the context of additional safety concerns that were presented in the original safety review. There was also an excess of cases of CHF, SVT/atrial fibrillation, pneumonia, as well as more discontinuations for skin and liver related events in the febuxostat group. In and of themselves, these issues would not preclude approval, but in the context of the CV issue, take on greater importance in the sense that the totality of the safety profile is not favorable for febuxostat.

It might also be possible that if the sponsor continues to pursue the higher doses, that the drug

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In the original approvable letter, there were 2 additional areas of concern, the first relating to analyses of PK interactions of febuxostat with theophylline, azathioprine or mercaptopurine, and the second relating to the potential for hemorrhagic events with concomitant warfarin administration. To address the first issue, the sponsor has agreed to a labeling contraindication for co-administration of theophylline or azathioprine/mercaptopurine with febuxostat.

For the second issue, the sponsor contends that: 1) based on clinical observations in over 40 patients taking concomitant warfarin in the phase 3 studies, febuxostat does not produce a clinically significant interaction with warfarin; 2) the phase 1 interaction study was conducted and analyzed correctly and multiple oral doses of febuxostat had no effect on the PK or PD of warfarin.

The clinical consequences of the use of warfarin in patients on febuxostat is difficult to interpret from the data presented. The initial NDA presented data on 2 patients who died with retroperitoneal hemorrhage. The first patient had a CT report that did not support a diagnosis of retroperitoneal hemorrhage, but did not rule out blood in the abdomen. The second patient likely did have a retroperitoneal hemorrhage but it is not clear if she was receiving febuxostat during her hospitalization. In the phase 3 trials one patient on allopurinol developed epistaxis. During the long term extension studies 2 patients on 80 mg febuxostat, one patient on febuxostat 120 mg and no patients on allopurinol developed at least one bleeding adverse event while on warfarin. For patients on warfarin before entering a trial, 3 patients had an increased PT on febuxostat 120 mg (25%) and

one on febuxostat 80 mg (9%) had an increased PT. vs one on allopurinol (11%). There are too few events to make any firm conclusions from the clinical data.

At this juncture, the issue of the potential for febuxostat to interact with warfarin appears to hinge on the adequacy of the warfarin interaction study. If the study as was performed previously is considered to be acceptable, then the sponsor can be asked to follow up with collection of phase 4 data to further evaluate this issue (discussions with OCPB indicates that the original study is acceptable and they will not require a repeat interaction study; final consult is pending at this time). If the warfarin interaction study is not acceptable, the sponsor should be required to perform another study to definitively address the issue of warfarin interaction with febuxostat. However, this may be done as a phase 4 commitment, _____

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One last point in regards to the warfarin issue. If we examine the warfarin label, there is a section that lists a number of drugs with the potential to interact with warfarin and lead to an increased INR or PT. Allopurinol is one such drug. _____

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Conclusions:

This NDA remains approvable.

In conclusion, there appears to be a potentially clinically significant increased incidence of CV events in the febuxostat treatment arm that warrants further study before this drug is approved. If another study is undertaken, the sponsor should incorporate both a DMC as well as a CV adjudication committee whose job is to independently review and adjudicate all cases. Every effort should be made to collect all safety related data and to followup all cases until the end of the trial. Furthermore, the use of febuxostat with theophylline or azathioprine should be contraindicated, and finally, _____

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/s/

Joel Schiffenbauer
7/17/2006 06:33:43 AM
MEDICAL OFFICER



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: May 12, 2006

From: Thomas A. Marciniak, M.D.
Medical Team Leader
Division of Cardiovascular and Renal Products (HFD-110)

Subject: Cardiovascular events with febuxostat, NDA 21-856

Through: Norman Stockbridge, M.D., Ph.D.
Division Director

To: Matthew Sullivan
Division of Anesthesia, Analgesia and Rheumatology Products (HFD-170)

This memo responds to your consult to us dated April 10, 2006, requesting that we perform a blinded adjudication of cardiovascular events in thirteen cases from the febuxostat development program. We have provided a brief summary of the adjudication criteria and a table with our adjudications, followed by some comments on the adjudication.

Case Adjudication

The material you provided claims that the assessments performed by the sponsor's consultant were based on the Antiplatelet Trialists' Collaboration (APTC) endpoints excluding GI hemorrhage (Antiplatelet Trialists' Collaboration 1994). The endpoints adjudicated were the following: (1) cardiac events – arrhythmias, acute coronary syndromes, angina pectoris, cardiac arrest, coronary revascularization including percutaneous transluminal angioplasty or coronary artery bypass graft surgery, congestive heart failure (HF), and acute myocardial infarction (MI); (2) deaths, including sudden/unexplained death or other cardiac death; and (3) cerebrovascular events – carotid stenosis or carotid revascularization, ischemic or hemorrhagic stroke, syncope, and transient ischemic attack. The following definitions were used for certain events: Acute myocardial infarction was defined as the presence of two of the following criteria: (1) chest pain or equivalent of a cardiac nature; (2) any abnormal value of creatine phosphokinase MB or troponin; (3) myocardial injury pattern or development of Q waves in two contiguous electrocardiographic leads. Stroke was defined as an acute, focal neurologic event lasting > 24 hours, with imaging studies used if available. Cardiovascular death was defined as sudden or explained death or those due to myocardial infarction, stroke, or pulmonary embolus. If the clinical data supported a different diagnosis from that of the original reporter, the event was reclassified. If the data available were insufficient to make a definitive diagnosis, then the

original reporter's diagnosis was accepted. When two events that were clinically linked occurred within 1-2 weeks of each other, only the more severe event was included—e.g., a stroke followed by death from stroke was analyzed only as a cardiovascular death.

We show our adjudications in the table below.

Table: Adjudication of Events for 13 Patients in the Febuxostat Development Program

| # | Study day ¹ | Event | Adequate info ² | Comment |
|------|------------------------|--------------------------------|----------------------------|---|
| 310 | 3 | CV death | Yes | Sudden death |
| 2019 | 49 | Worsening HF | Yes | |
| | 161 | Worsening HF | No | Per investigator |
| | 287 | Non-CV death | Yes | Retroperitoneal bleed |
| 2223 | 313 | MI | No | Per investigator |
| | 314 | Coronary revasc ³ | No | Angioplasty |
| 2403 | 169 | Carotid revasc | Yes | |
| | 170 | CV death | Yes | Cardiac arrest post-op |
| 2487 | 81 | Worsening HF | No | In setting of respiratory & renal failure |
| 2790 | 628 | Stroke | No | MRI diagnosed |
| 4186 | 406 | Atrial arrhythmia | Yes | New onset atrial fib |
| | 417 | Atrial arrhythmia ³ | Yes | Tachybrady syndrome |
| | 432 | Non-CV death | Yes | Retroperitoneal bleed |
| 4479 | 12 | CV death | No | Sudden death, inadequate info on MI |
| 4665 | 21 | (None) | No | Hypoglycemic seizure; troponin leak |
| 4730 | 552 | MI | No | Per investigator |
| | 552 | Coronary revasc ³ | No | Stent placement |
| 4959 | 13 | Worsening HF | Yes | With pneumonia, inadequate info for HF |
| 4963 | 84 | MI | No | Per investigator |
| | 84 | Coronary revasc ³ | No | Coronary stent |
| 5000 | 185 | MI | Yes | |

CV = cardiovascular; HF = heart failure; MI = myocardial infarction; revasc = revascularization

¹Study day of current study; patients may have been treated in earlier studies

²Whether information provided was adequate to apply criteria or otherwise confirm event

³Less serious or second of related events

Comments

The material provided did not provide complete definitions or diagnostic criteria for most events. In particular, congestive heart failure (HF) is a chronic disease, not an event. We interpreted this term to mean new onset of HF or acute exacerbation of existing HF. Also, arrhythmias are mentioned without any definition or discussion of the types of arrhythmias. We have qualified arrhythmias that we adjudicated as atrial arrhythmias—there were no documented ventricular arrhythmias reported in these cases (although, of course, the cardiac arrests probably represent ventricular arrhythmias.)

We found these adjudications to be largely an exercise in futility: Between lacking criteria for most events and lacking clinical information for most criteria, we do not consider these

adjudications to be very helpful. For example, of the five possible MI events (six counting the sudden death attributed to an MI), for only one did the case report form provide sufficient information on all three MI criteria categories to adjudicate the event—and even that case remains arguable. For most cases we followed the adjudication rule that, if there was insufficient information to change the diagnosis, we accepted the investigator's diagnosis.

While reliable adjudication of these cases is not possible with the case report forms provided, we think that precise adjudication is not needed. The case report forms provide reasonable documentation that these events were serious and, for all but one (case 4665), that they were cardio/cerebrovascular in nature. We believe that you should count them as we have classified them in the table above for any initial evaluations of the cardiovascular safety of febuxostat.

We have one additional set of comments: While the sponsor refers to their criteria as "APTC" criteria, we find little in common with the original APTC definitions. The APTC definitions used for the original APTC meta-analysis were terms for thromboembolic and bleeding events used to provide some commonality among the many endpoints used in the studies included in the meta-analysis. The APTC group was unable to specify optimal, detailed criteria (because the supporting data were not collected prospectively), to collect more information on the cases, or even to re-adjudicate them—the APTC group was forced by practicality to accept the diagnoses used in the original studies. The sponsor has extended the APTC endpoints into many other domains (e.g., arrhythmias, revascularization, and heart failure) and provided more detailed and updated criteria for some events, e.g., MI. These extensions (and more!) are appropriate and are needed to make the adjudication useful for an analytic situation in which one can examine the individual patient case reports. The criteria as provided remain too ambiguous for adjudication of most of the events, and we would not attach any credibility to them because the sponsor has labeled them as "APTC". While the criteria are weak, the larger problem remains the lack of detail in the case report forms.

Recommendations

Please see the Table above for our recommendations on classifying the 13 cases.

Reference

Antiplatelet Trialists' Collaboration (1994). "Collaborative overview of randomised trials of antiplatelet therapy Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients." BMJ 308(6921): 81-106.

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/s/

Thomas Marciniak
5/12/2006 08:55:13 AM
MEDICAL OFFICER

Norman Stockbridge
5/15/2006 10:25:08 AM
MEDICAL OFFICER



FDA CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ANESTHESIA, ANALGESIA AND RHEUMATOLOGY PRODUCTS
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DIVISION DIRECTOR SUMMARY REVIEW AND BASIS FOR APPROVABLE ACTION

DATE: October 114, 2005

DRUG: Uloric (febuxostat, 80-mg and 120-mg tablets)

NDA: 21-856

NDA Code: Type 1S NDA

SPONSOR: TAP Pharmaceutical Products, Inc.

INDICATION: For the management of hyperuricemia in patients with gout

TAP Pharmaceutical Products submitted NDA 21-856 in support of marketing approval for Uloric, (febuxostat, 80-mg and 120-mg tablets), on December 15, 2004.

Review of the CMC portion of this application was completed by Sue-Ching Lin, Ph.D. Review of the pharmacology and toxicology data presented in this application was completed by Asoke Mukherjee, Ph.D. Review of the clinical pharmacology and biopharmaceutics data in the application was completed by Lei Zhang, Ph.D, E. Dennis Bashaw, Pharm.D, (Drug Interaction Studies) and V. Atul Bhattaram, Ph.D. (Pharmacometrics). A statistical review and evaluation was completed by Mohammad Atiar Rahman, Ph.D. The clinical safety review was completed by Tatiana Oussova, M.D. and review of the efficacy data, in addition to a secondary review of the safety data. was completed by Joel Schiffenbauer, M.D. A supervisory summary review of the clinical data was submitted by Sharon Hertz, M.D. Consultation on this application was also obtained from the Division of Drug Marketing, Advertising and Communications (DDMAC) and the Office of Drug Safety (ODS).

Uloric is a non-purine selective inhibitor of xanthine oxidase (XO) that inhibits the formation of uric acid from xanthine. Uloric is a more specific inhibitor of XO than allopurinol, the only approved XO inhibitor, having minimal effect on the other enzymes involved in purine and pyrimidine metabolism. The sponsor has demonstrated the efficacy of Uloric in two adequate and well-controlled trials, as reviewed by Drs. Schiffenbauer and Rahman. Therefore, I will only briefly summarize the trials in this memo. In their reviews of the safety data, Drs. Oussova, Schiffenbauer and Hertz each noted concern regarding the safety profile of Uloric, and they have recommended that the product not be approved until a more complete assessment of safety has been performed, and a more reasonable risk to benefit ratio has been established.

Efficacy:

Study 009:

This was a randomized, double-blind, multicenter, active and placebo-controlled, parallel-group trial which compared single doses of Uloric 80mg, 120 mg or 240 mg to allopurinol (100 mg or 300 mg) and placebo in adult subjects with gout. Subjects with serum urate levels greater than or equal to 8.0 mg/dL were randomized to the above noted arms and, after a washout/run-in period, treated for 28 weeks with study medication. The subjects randomized to the allopurinol treatment received either 100 mg or 300 mg based on their creatinine clearance rates. The randomization ratio was 1.2.2.1.2 for the placebo subjects, Uloric 80-mg, 120-mg, and 240-mg subjects, and allopurinol 300 mg and 100 mg subjects, respectively.

The primary efficacy variable was the proportion of subjects whose last three serum urate levels were less than 6.0 mg/dL. Subjects who discontinued from the study prior to having had three serum urate levels documented were considered non-responders. A sequential statistical analysis series was performed on the data collected for this endpoint.

Steps:

1. Each Uloric arm was compared to placebo. If each of the comparisons showed a statistically significant treatment effect, the procedure proceeded to Step 2.
2. Binomial 97.5% confidence intervals were calculated for the differences in response rates between each of the Uloric arms and the combined Allopurinol arms. Non-inferiority to allopurinol was declared if the absolute value of the lower bound of the confidence interval did not exceed 10%.
3. Each Uloric group that was found to be non-inferior to the allopurinol group in Step 2 was compared to the allopurinol group to test for superiority.

Secondary efficacy measures included:

- The proportion of subjects whose serum urate levels were less than 6.0 mg/dL

- The percent reduction in serum urate levels
- The percent reduction in primary tophus size, as determined by physical measurement in the subset of subjects with a primary palpable tophus at screening
- The reduction in the total number of tophi in the subset of subjects with palpable tophi at screening
- The proportion of subjects requiring treatment for a gout flare between Weeks 8 and 28

Dr. Schiffenbauer's Table 35 (page 85 of his review) summarizes the results for the primary outcome analysis and has been reproduced below:

Table 35 : Proportion of Subjects Whose Last 3 Serum Urate Levels were <6 mg/dl- ITT subjects

| Last 3 Serum Urate Levels | Placebo | | Febuxostat 80 mg QD | | Febuxostat 120 mg QD | | Febuxostat 240 mg QD | | Allopurinol 300/100 mg QD | |
|---------------------------|----------------|------|----------------------------------|-----|----------------------------|-----|-------------------------------|-----|---------------------------|-----|
| | n/N | (%) | n/N | (%) | n/N | (%) | n/N | (%) | n/N | (%) |
| <6.0 mg/dL | | | | | | | | | | |
| Yes | 0/134 | (0%) | 126/262 (48%) ^{†,‡,§,¶} | | 173/269 (65%) [†] | | 92/134 (69%) ^{†,§,¶} | | 60/268 (22%) [†] | |
| No | 134/134 (100%) | | 136/262 (52%) | | 94/269 (35%) | | 42/134 (31%) | | 208/268 (78%) | |
| | | | Difference in Proportions | | 97.5% CI [†] | | | | P-value [‡] | |
| | | | 26% | | (16.7%, 34.7%) | | | | <0.001 ^a | |
| | | | 43% | | (34.0%, 51.3%) | | | | <0.001 ^a | |

† 97.5% CI = 97.5% confidence interval for the difference in proportions based on the normal approximation for the binomial distribution

‡ P-values from a CMH test stratified by baseline renal function (serum creatinine ≤1.5 mg/dL vs. >1.5 mg/dL)

§ Statistically significant difference versus allopurinol 300/100 mg QD at the 0.05 level using Hochberg's procedure for multiple comparisons

¶ Statistically significant difference versus placebo (p≤0.05) (Hochberg's procedure for multiple comparisons was used for comparisons of the febuxostat treatment groups versus placebo)

^a Statistically significant difference versus allopurinol 300/100 mg QD (p≤0.05).

^m Statistically significant difference versus febuxostat 120 mg QD (p≤0.05).

^h Statistically significant difference versus febuxostat 240 mg QD (p≤0.05).

Cross-reference: Statistical Table 14.2.1.1 and Appendix 16.2-6.1.1

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These results clearly reveal a statistically significant treatment effect for each dose of Uloric in comparison to placebo and in comparison to the allopurinol groups.

The results of the secondary analyses were generally supportive of the primary outcome assessment. While the effects on tophus size reduction, the number and timing of gouty flares and quality of life scores were not impressive, there did seem to be a trend towards a positive clinical effect for Uloric compared to placebo that was time and dose related.

Study 010:

This was a randomized, double-blind, multicenter, active-controlled, parallel-group trial which compared single doses of Uloric 80mg and 120 mg to allopurinol 300 mg in adult subjects with gout. Subjects with serum urate levels greater than or equal to 8.0 mg/dL were randomized to the above noted arms and, after a washout/run-in period, treated for 52 weeks with study medication. The randomization ratio was 1.1.1.

The primary efficacy variable was the proportion of subjects whose last three serum urate levels were less than 6.0 mg/dL. Subjects who discontinued from the study prior to having had three serum urate levels documented were considered non-responders. A sequential statistical analysis series was performed on the data collected for this endpoint.

Steps:

1. Binomial 97.5% confidence intervals were calculated for the differences in response rates between each of the Uloric arms and the allopurinol arm. Non-inferiority to allopurinol was declared if the absolute value of the lower bound of the confidence interval did not exceed 10%.
2. Each Uloric group that was found to be non-inferior to the allopurinol group in Step 2 was compared to the allopurinol group to test for superiority.

Secondary efficacy measures included:

- The proportion of subjects whose serum urate levels were less than 6.0 mg/dL
- The percent reduction in serum urate levels
- The percent reduction in primary tophus size, as determined by physical measurement in the subset of subjects with a primary palpable tophus at screening
- The reduction in the total number of tophi in the subset of subjects with palpable tophi at screening
- The proportion of subjects requiring treatment for a gout flare between Weeks 8 and 52

Dr. Schiffenbauer's Table 66 (page 132 of his review) summarizes the results for the primary outcome analysis and has been reproduced below:

Table 66 : Proportion of Subjects Whose Last 3 Serum Urate Levels were <6.0 mg/dL - ITT Subjects

| | Febuxostat 80 mg QD | Febuxostat 120 mg QD | Allopurinol 300 mg QD |
|--|----------------------------------|---------------------------------|----------------------------------|
| Last 3 Serum Urate Levels <6.0 mg/dL | n/N (%) | n/N (%) | n/N (%) |
| Yes | 136/255 (53%) | 154/250 (62%) | 53/251 (21%) |
| No | 119/255 (47%) | 96/250 (38%) | 198/251 (79%) |
| | Difference in Proportions | 97.5% CI^a | P-value^b |
| Febuxostat 80 mg vs. Allopurinol | 32% | (23.1%, 41.3%) | <0.001 ^{&} |
| Febuxostat 120 mg vs. Allopurinol | 41% | (31.5%, 49.5%) | <0.001 ^{&} |

a 97.5% confidence interval for the difference in proportions based on the normal approximation for the binomial distribution

b P-values from the Fisher's exact test

& Statistical significance versus allopurinol 300 mg QD at the 0.05 level based on Hochberg's procedure for multiple comparisons

Statistical Table 14.2.1.1

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As in Study 009, these results clearly reveal a statistically significant treatment effect for each dose of Uloric in comparison to the allopurinol group, and the results of the secondary analyses were generally supportive of the primary outcome assessment. Again, while the effects on tophus size reduction, the number and timing of gouty flares and quality of life scores were not impressive, there did seem to be a trend towards a positive clinical effect for Uloric that was time and dose related.

Clinical Safety:

A total of 2,531 subjects were exposed to Uloric in the clinical development program. Dr. Hertz's Cumulative Extent of Exposure table on page 2 of her review summarizes the actual data with regard to exposure by dose and duration. Of note, there were nearly three-fold as many patients exposed to Uloric compared to allopurinol, and ten-fold as many patients exposed to Uloric compared placebo, in the Phase 2 and 3 studies.

All eight deaths occurred in subjects exposed to Uloric. Two patients, one each on 80 and 120 mg, died after documented retroperitoneal hemorrhages. Both of these patients were receiving concomitant treatment with warfarin. Two patients had myocardial infarctions which led to their deaths after extended treatment with Uloric. As Dr. Hertz notes on page 4 of her review:

The patient population under study, patients with gout, is one that often has risk factors for cardiovascular disease, the deaths due to MI and respiratory failure all occurred in patients who were exposed to febuxostat, but given the limited exposure to comparators and the low overall number of events, it is difficult to know if these events were more likely to occur and to result in death due to the exposure to febuxostat.

There were several serious adverse events (SAEs) that occurred with greater frequency in the Uloric-treated subjects. These included: pneumonia, small intestinal obstruction, prostate cancer, exacerbation of COPD, acute renal failure, CVA, respiratory failure, metastatic colon cancer, and deep vein thrombosis. Only diverticulitis and osteoporosis were more common in the allopurinol-treated subjects. In studies performed in Japan with lower doses of Uloric (10, 20 and 40 mg) than those used in the U.S. studies, there were eleven SAEs including: stomach discomfort, respiratory tract inflammation, elevated LFTs, intracerebral hemorrhage, tendon/ligament ruptures, pain, gout flares, and tonsillitis. There were two cases of acute renal failure in Uloric-treated subjects and none in allopurinol or placebo-treated subjects.

Dr. Hertz analyzed the incidence of cardiac SAEs (ischemic events, arrhythmias, congestive failure, cardiomyopathy and ventricular rupture) in the Phase 2 and 3 studies. She found a similar incidence of events in the combined Uloric-dose groups and the allopurinol group. Only one cardiac event occurred in a placebo-treated subject. She also analyzed the cardiac ischemia SAEs separately and found that there were proportionately

more events in the Uloric-treated subjects (0.8%) compared to the allopurinol-treated subjects (0.2%). There was no apparent dose response in the Uloric groups.

Dr. Hertz also found that there were proportionately more CVAs in the Uloric-treated subjects (0.4%) compared to the allopurinol or placebo-treated subjects (0 events in each). When she analyzed the incidence of combined MI, CVA and cardiac arrest events, she found that there was a higher incidence of these events in the Uloric-treated subjects (1.1% and 0.9% in the 120 mg and 80 mg-treated subjects, respectively) compared to the allopurinol-treated subjects (0.2%). It is important to note that two of the subjects, one with MI and one with angina, had received allopurinol prior to treatment with Uloric.

Dr. Hertz also analyzed the incidence of atrial fibrillation listed as SAEs in the database. The incidences were 0.7% in the Uloric 80 mg-treated subjects, 0.3% in the Uloric 30 mg-treated subjects, and 0.5% in the allopurinol-treated subjects.

Dr. Hertz found that the overall rate of treatment emergent adverse events leading to discontinuation ranged from 4% to 9%, with Uloric-treated subjects having the highest rate. In her review, she notes that the most common adverse event leading to early discontinuation was elevated LFTs, particularly in the Uloric 240-mg group, but also occurring somewhat more frequently in the Uloric 80-mg and 120-mg groups. Diarrhea was also more common in the Uloric 240-mg group. Abnormal renal function leading to discontinuation occurred with equal frequency in the Uloric and allopurinol groups.

Rash reported as macular or maculo-papular, as an adverse event leading to discontinuation, occurred in a total of eight (<1%) subjects on any dose of Uloric, three in subjects who received Uloric 80 mg and five in subjects who received Uloric 120 mg. There were no reports of macular or maculo-papular rash in allopurinol-treated subjects. Rash reported as papular and leading to discontinuation occurred in four (<1%) patients who received any dose of Uloric and no patients who received allopurinol. Rash reported as erythematous and leading to discontinuation occurred in two (<1%) patients who received allopurinol and no patients who received Uloric.

There was a single case of idiopathic thrombocytopenic purpura in a subject who had received Uloric 80 mg and one case of angioneurotic edema in a subject who had received Uloric 120 mg. There were 19 patients who discontinued due to adverse events in studies conducted in Japan; the events included elevated liver function tests and rash. The overall incidence of discontinuations due to adverse events was lower during periods of the studies that excluded the use of colchicine. Colchicine is known to be associated with nausea and diarrhea.

Upper respiratory infections, musculoskeletal and connective tissue signs and symptoms, joint-related signs and symptoms, diarrhea, and headaches were the most common adverse event groupings in Uloric-treated subjects and were more common than in allopurinol-treated subjects. Neurological signs and symptoms (dizziness, dysgeusia, hypogeusia, and Tinel's sign), elevated LFTs, nausea and vomiting, and hypertension were more common

in Uloric-treated subjects. There were no consistent dose responses for these adverse events across the Uloric treatment groups. LFT elevations appeared to be of greater magnitude in the Uloric treatment groups, but these were predominantly isolated AST elevations. The incidence of renal adverse events was comparable across treatment groups.

Nonclinical Safety:

There were no clinically relevant nonclinical safety findings.

Clinical Pharmacology and Biopharmaceutics:

The current dissolution method and acceptance criterion are not acceptable. Dr. Zhang has recommended that the sponsor test the dissolution of Uloric using USP Apparatus 2 (paddle) at 75 rpm with 900 mL of 0.05 M potassium phosphate buffer, pH 6.8, maintained at 37°C, with an acceptance criterion of Q equal to — , at 15 minutes.

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Dr. Zhang has also recommended that the sponsor be required to perform in vivo drug-drug interaction studies with theophylline, mecaptopurine, and azathioprine, (or contraindicate their co-administration with Uloric), because these drugs are substrates for XO and, as Uloric is a potent inhibitor of XO and Allopurinol, a much weaker XO inhibitor, showed a clinically significant in vivo inhibition effect on these drugs, the effect of co-administration with Uloric cannot be any less and, in fact, may be more pronounced. Therefore, without an in vivo drug interaction study, it would not be possible to make dosing recommendations for the safe administration of these drugs together with Uloric.

In Dr. Bashaw's review of a drug-drug interaction study with Uloric and warfarin, he found that eight subjects were discontinued from the study due to high INR values and were given Vitamin K, and an additional subject was administered Vitamin K at the end of the study due to increased INR values. In his analysis of the data, he found that, although an equivalent number of subjects were discontinued for high INR values during both the Uloric and the placebo phases of the study, the highest INR value occurred during the placebo phase. If this subject was removed from the database, the resulting values for the placebo arm would be markedly reduced. He concludes that, although it is necessary to include all of the data in a small study such as this, there is not enough data to say that these findings are not of concern. The study conduct was inconsistent in the handling of Vitamin K administration and, while the mean data may seem similar, the actual individual data does indicate that a deeper look is needed, especially in light of the reports of retroperitoneal and other hemorrhages in the clinical trials database.

Chemistry, Manufacturing and Controls:

Based on these clinically relevant safety concerns, and the unclear balance of risk and benefit that these concerns warn of, the sponsor should perform further clinical evaluations to better delineate the cardiovascular safety profile of Uloric, the potential for hemorrhagic AEs, and the potential for drug-drug interactions with commonly co-administered drug products. Additionally, the sponsor should adopt the dissolution method and dissolution specification following the recommendations of the clinical pharmacology and biopharmaceutics review team.

Finally, Dr. Schiffenbauer has recommended that the sponsor complete further studies to evaluate clinical endpoints. Although the recommendations of the Arthritis Advisory Committee and the available literature support the use of serum uric acid levels as a surrogate endpoint, the Advisory Committee members also recommended that trials to assess actual clinical outcomes should be undertaken for drugs used to treat gout. As Dr. Thomas Permutt, Team Leader for the biostatistics team, noted in a personal communication:

A surrogate that is qualitatively related to clinical outcome may be enough to show that a drug is effective. Nevertheless, if questions of risk and benefit arise, the magnitude, not just the existence, of the correlation may become critical.

We might be quite confident that a change in uric acid is associated with some clinical improvement, without being confident of how much clinical improvement to expect. If so, we might still require evidence that the clinical benefit was enough to justify the risk.

Therefore, the sponsor should be asked to perform studies that demonstrate a clear clinical effect. While not required for approval of this application, these studies should be required as a Phase 4 commitment.

Action:

Approvable

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II, CDER, FDA

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Bob Rappaport
10/14/2005 01:59:20 PM
MEDICAL OFFICER

Robert Meyer
10/14/2005 02:17:18 PM
MEDICAL OFFICER

I am in substantial agreement with Dr. Rappaport's memo
and consider this to be the memorandum of
record for this action cycle leading to an
approvable action.

9/23/05

SAFETY
CLINICAL REVIEW

Application Type NDA #21-856
Submission Number 000
Submission Code N

Letter Date 12/14/04
Stamp Date 12/15/04
PDUFA Goal Date October 15, 2005

Reviewer Name Tatiana Oussova, M.D.
Review Completion Date 09/09/05

Established Name Uloric
(Proposed) Trade Name Febuxostat
Therapeutic Class Xanthine oxidase inhibitor
Applicant TAP Pharmaceutical Products Inc.

Priority Designation S

Formulation Oral
Dosing Regimen 80 mg and 120 mg tablets once a
day
Indication Management of hyperuricemia in
patients with gout
Intended Population Adults

Clinical Review
Tatiana Oussova, MD
NDA 21-856
Febuxostat (Uloric)

**APPEARS THIS WAY
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ON ORIGINAL**

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1 EXECUTIVE SUMMARY

Please, see medical officer review by Dr. Schiffenbauer

2 INTRODUCTION AND BACKGROUND

Please, see medical officer review by Dr. Schiffenbauer

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

Please, see medical officer review by Dr. Schiffenbauer

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

Please, see medical officer review by Dr. Schiffenbauer

5 CLINICAL PHARMACOLOGY

Please, see medical officer review by Dr. Schiffenbauer and specialty reviews by Lei Zhang, Ph.D., Dennis Bashaw, Pharm. D., V. Atul Bhattaram, Ph.D.

6 INTEGRATED REVIEW OF EFFICACY

This portion of the submission has been reviewed by Dr. Schiffenbauer

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Safety evaluation was performed by reviewing ISS and safety data from individual trials. This safety review was updated after receiving 120-days safety update. New data in this update are from 2 ongoing studies: TMX-01-005 and C02-021. Data collection from these studies is ongoing. Safety data, collected until 15 September 2003 for an interim analysis of TMX-01-005 and until 30 April 2004 for an interim analysis of C02-021, were included in the original ISS.

Safety data collected until 29 October 2004 for both Studies TMX-01-005 and C02-021 are included in this update. SAEs reported from 30 October 2004 to 31 December 2004 are listed in Section 3.4.1.4, but are not included in the integrated analyses.

The doses of febuxostat being proposed for marketing in this application are 80 mg or 120 mg to be taken once daily (QD).

The objective of the United States febuxostat clinical development program was to demonstrate that febuxostat could safely and effectively manage hyperuricemia in patients with gout. The United States clinical program for febuxostat included 24 Phase 1 trials (including 1 study each conducted in hepatic and renal impaired subjects), 2 Phase 2 trials (including 1 dose-ranging study), and 3 Phase 3 trials in subjects with a history or presence of gout defined by the preliminary criteria of the American Rheumatism Association (ARA) for the classification of the acute arthritis of primary gout and a serum urate level ≥ 8.0 mg/dL.

Of note, interim safety and efficacy data from one of the Phase 3 controlled studies, an ongoing 24-month, extension trial (C02-021) and from one of the Phase 2 studies, an ongoing intended 5-year, extension trial (TMX-01-005) are included in this application.

The Japan program for febuxostat included six Phase 1 trials, seven Phase 2 trials, and two Phase 3 trials. However, since the Japan program evaluated lower doses of febuxostat (doses up to 40 mg QD) than those being developed in the United States (80 mg QD and 120 mg QD) and a different demographic population, these studies are considered supportive for safety. Therefore, the discussion of safety data from all Japanese studies in this Integrated Summary of Safety (ISS) is limited to information on serious adverse events and premature discontinuations due to adverse events.

Throughout the US clinical program, the safety of febuxostat was assessed by adverse events, physical examinations, laboratory evaluations, vital signs, and electrocardiograms (ECGs). Rashes were carefully monitored and documented on the case report form as well as a Rash Adverse Event Worksheet.

The potential effect of febuxostat on cardiac repolarization as assessed by QTc interval was also evaluated in a Phase 1 study utilizing moxifloxacin as a positive control (Study C02-023 Part B).

Adverse events of special interest (cardiovascular, hypertension, gastrointestinal, renal, lipid metabolic, thyroid, rash, hepatic, neurological, and hematological adverse events) were summarized for the Phase 3 controlled and Phase 2/3 studies. These organ systems were selected because of the known high prevalence of certain comorbidities in the gout population (cardiovascular disease, hypertension, renal and lipid disorders) or because of known side effects (cutaneous rash, hepatotoxicity, bone marrow toxicity) of the only other available XO inhibitor, allopurinol. Finally, additional organ systems were added because of findings in the febuxostat preclinical (thyroid effects) or clinical (diarrhea, nausea, and one event of Guillain-Barré syndrome) program.