CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-856

CROSS DISCIPLINE TEAM LEADER REVIEW

FDA Center for Drug Evaluation and Research
Office of New Drugs
Office of Drug Evaluation 2
Division of Anesthesia, Analgesia and Rheumatology Products

Addendum to Cross-Discipline Team Leader (CDTL) Memorandum

Date: February 11, 2009

To: File, NDA 21-856

From: Jeffrey Siegel, M.D.
Clinical Team Leader
ODE2 - Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)

Re: Pediatric waiver
Financial disclosure for Study F-GT06-153

This memorandum will address two issues concerning the Uloric (febuxostat) NDA application: the decision to grant a waiver for pediatric studies under PREA and financial disclosure for Study F-GT06-153.

Regarding the need for pediatric studies, under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable. The claimed indication for febuxostat is the management of hyperuricemia in patients with gout, which is extremely rare in individuals below 18 years of age. The Pediatric Review Committee (PeRC) met on 12/10/08 and agreed to grant a full pediatric waiver for febuxostat (Uloric) for the management of hyperuricemia in patients with gout.

Concerning financial disclosure for Study F-GT06-153, the Applicant submitted financial disclosure information for the study. None of the investigators or subinvestigators had potential financial conflicts.

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

/s/

Jeffrey N Siegel
2/11/2009 11:37:33 AM
MEDICAL OFFICER

Cross-Discipline Team Leader Memo

FDA Center for Drug Evaluation and Research
Office of New Drugs
Office of Drug Evaluation 2
Division of Anesthesia, Analgesia and Rheumatology Products

Cross-Discipline Team Leader Memorandum

Date: December 31, 2008

To: File, NDA 21-856

From: Jeffrey Siegel, M.D.
Clinical Team Leader
ODE2 - Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)

Re: NDA 21-856
ULORIC® (febuxostat)
Takeda, Inc.
Proposed indication: Hyperuricemia in patients with gout

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1. Introduction to Review

Takeda submitted a new drug application (NDA) for a new molecular entity, febuxostat (ULORIC), for the treatment of hyperuricemia in patients with gout. Febuxostat is a xanthine oxidase inhibitor that lowers uric acid levels by inhibiting the conversion of xanthine to uric acid. The Applicant originally submitted safety and efficacy data from two randomized, controlled Phase 3 trials using an 80 mg and a 120 mg po qd regimen. Although the Agency determined that data from those trials demonstrated efficacy of the 80 mg and 120 mg doses, review of safety data suggested that treatment with febuxostat was associated with a higher rate of cardiovascular thromboembolic events. Consequently, the Agency issued an Approvable letter citing the cardiovascular safety signal as an issue that would need to be addressed before ULORIC could be approved. The Applicant subsequently submitted a Complete Response with a reanalysis of the cardiovascular safety data. This submission also resulted in an Approvable action. The Approvable letter again cited the cardiovascular safety signal. The current submission represents the third cycle for this NDA. It contains the results of a third Phase 3 trial that addresses safety and efficacy of the 80-mg dose as well as a lower, 40-mg dose.

During the review of this submission, important issues arose concerning the cardiovascular safety of febuxostat and concerning the inspection of the manufacturing plant for the drug substance. The cardiovascular safety issue relates to the fact that in the initial two Phase 3 trials there was a higher rate of cardiovascular thromboembolic events. Although the third Phase 3 trial did not demonstrate a cardiovascular safety signal the study was not adequately designed to exclude a moderate increase in the rate of cardiovascular events with febuxostat. The issue concerning the manufacturing plant relates to the fact that, although the Applicant has enough drug substance to market ULORIC [redacted] from a previously inspected plant, that plant was subsequently demolished and the Applicant has not designated a new manufacturing facility. This memo will review the regulatory background for this submission, data concerning the cardiovascular safety of febuxostat both from the earlier Phase 3 trials and the new trial, safety and efficacy data from the new Phase 3 trial as well as key findings from other disciplines. b(4)

2. Background – Regulatory history

Gout

Gout is an arthropathy associated with the deposition of uric acid crystals in joints and other tissues that can present both with acute and with chronic manifestations. In its acute form gout presents as a highly inflammatory arthritis, classically involving the great toe, manifest as pain, swelling and other signs of inflammation. Gout can also evolve as a chronic condition, manifest as recurrent episodes of arthritis as well as by tophi, deposits of uric acid crystals in various tissues. Gout is estimated to affect between 3 and 5 million people in the United States. It predominantly affects men, although gout is also seen in women with an incidence increasing with advancing age.

A cardinal feature of gout is hyperuricemia. A serum urate of 7.0 mg/dL or greater is a diagnostic criterion. Although not all individuals with elevated serum uric acid develop gout, the risk of developing gout increases with increasing serum uric acid over 7.0 mg/dL. Over time with elevated serum urate levels the total body burden of uric acid increases, which can lead to deposition of uric acid as tophi and recurrent episodes of gouty arthritis. Treatment for acute episodes of gout include anti-inflammatory medications, such as non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and, to a lesser extent, colchicine. Treatment for chronic gout is directed at preventing acute episodes of gouty arthritis with colchicine and at lowering elevated serum urate levels to a level of 6.0 mg/dL or lower with the xanthine oxidase inhibitor allopurinol and, less commonly, with uricosuric agents. A frequent and well-documented complication of urate lowering therapies is precipitation of flares of acute gout. Therefore, prophylaxis using colchicine during the initiation of urate-lowering therapy is recommended.

When uric acid levels are effectively lowered over time, total body uric acid is decreased, tophi resorb and episodes of acute gout decrease in frequency. However, for a variety of reasons, urate-lowering therapy is frequently inadequate. Allopurinol at the usual starting dose of 300 mg daily is effective at lowering urate levels to below 6.0 mg/dL in only a fraction of patients. Although the label for allopurinol allows dosing of up to 800 mg daily most clinicians avoid higher doses for several reasons, including the association of allopurinol with rare but serious skin reactions. In addition, for patients with concomitant renal impairment, clinicians generally dose allopurinol at lower levels (e.g., 200 mg daily) because clearance is reduced in patients with renal impairment and because of a fear of serious skin reactions with higher doses. Thus, there is a need for additional urate-lowering therapies for chronic gout.

Another important feature of gout that is relevant to this application is an increased risk of cardiovascular disease. The precise explanation for this association remains under investigation but several studies have established a relative risk of 1.5 or greater. Patients with hyperuricemia are at increased risk of metabolic syndrome, hypertension, diabetes, chronic renal insufficiency and cardiovascular disease. One potential explanation is a possible increase in xanthine oxidase activity since xanthine oxidase is associated with an increased risk of hypertension and cardiac disease in experimental animals. Another explanation is that uric acid itself may have harmful effects, including deleterious effects on endothelial function. Despite the well-established association between hyperuricemia and cardiovascular disease no studies have yet demonstrated a cardiovascular benefit for lowering serum uric acid or for inhibiting xanthine oxidase. Another possible explanation for the association between gout and cardiovascular disease is a direct effect of uric acid on increasing cardiovascular risk, including a deleterious effect of elevated urate levels on endothelial function.

Regulatory History

When the Applicant originally submitted the NDA for febuxostat Agency review determined that there was adequate evidence of efficacy for the 80 mg and 120 mg doses; however, analysis of cardiovascular deaths and serious adverse events indicated a

cardiovascular safety signal in the 6-month duration of the two Phase 3 trials. Therefore, the Agency issued an Approvable letter stating that more information was necessary to address the apparent cardiovascular safety signal, either from a reanalysis of existing data or from a new trial. In the second submission, the Applicant provided a reanalysis of the data from the same clinical trials. Following review of the second submission the Agency determined that the evidence still suggested a cardiovascular safety signal. Therefore, the Agency issued a second Approvable letter, which stated that for ULORIC to be approved the Applicant would need to submit additional data to clarify the cardiovascular safety of the proposed 80 mg and 120 mg doses or to provide safety and efficacy data for lower doses.

Subsequently, the Applicant submitted a protocol for a randomized, double-blind, active control, 6-month trial comparing febuxostat 40 mg and 80 mg to allopurinol. In internal discussions concerning the new protocol the review division, DAARP, considered the potential outcomes of such a study and how they could be interpreted. If the 80 mg febuxostat dose demonstrated a higher rate of cardiovascular serious adverse events (SAEs) than allopurinol but the 40 mg dose was similar to allopurinol this would confirm the cardiovascular signal with the higher dose and suggest that the 40 mg dose was safer. However, if the new trial showed a similar rate of cardiovascular SAEs with febuxostat 80 mg as with allopurinol this would fail to confirm the earlier signal and could make the trial difficult to interpret. A new trial that failed to showed a cardiovascular safety signal with febuxostat 80 mg could mean that the previous apparent cardiovascular safety signal was spurious, but it could also raise questions as to whether the trial was adequately designed to detect such a signal. The review division (DAARP) told the Applicant that if no cardiovascular signal was seen with either the 80 mg or the 40 mg dose this would be potentially reassuring but it would be important to have enough cardiovascular SAEs in the trial overall to make conclusions about the cardiovascular safety of febuxostat.

3. CMC/Microbiology/Device

3.1. General product quality considerations

The CMC review team determined that so long as Compliance judges the application to be acceptable that febuxostat can be approved. The deficiencies identified in the earlier two review cycles were addressed adequately by the Applicant in the current submission, with the exception of issues concerning the discriminatory ability of the dissolution method for the two strengths. This issue was addressed by the Applicant by changing the pH of the media used in the method. The validation for this method was judged to be acceptable by the CMC reviewer.

3.2. Facilities review/inspection

There were no changes to the manufacturing facilities for febuxostat for the current submission as compared to the previous submissions. All facilities used in the manufacture and control of febuxostat were acceptable in the two previous cycles on 8/1/05 and 6/14/06, respectively. When inspectors went to the manufacturing site for the drug substance during the review of this submission they found that the plant had been

demolished. The Applicant states that they have enough drug substance to supply product for marketing ——— and that they will establish a new manufacturing facility for drug substance after febuxostat is approved. As of the time of writing of this memorandum, Compliance was discussing whether it is acceptable for febuxostat to be approved based on the earlier inspections or whether the absence of a plant for manufacture of drug substance is an approvability issue. b(4)

4. Nonclinical Pharmacology/Toxicology

As of the time of writing of this review the pharmacology/toxicology review had not been completed. In previous cycles, the pharmacology/toxicology review team determined that there were no issues that would prevent an approval. Verbally the pharmacology/toxicology review team for the current submission stated that they also had no issues that would prevent an approval. They also stated that there were no findings of cardiovascular toxicity in the animals tested.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology review team determined that the application is acceptable and may be approved so long as the Applicant and the Agency can agree on acceptable wording for the package insert. In the Approvable letter for the August 2, 2006 action, the Agency requested a febuxostat-warfarin interaction study and an in vitro study of the induction potential of febuxostat on primary human hepatocytes. In this submission the Applicant submitted the results of a febuxostat-warfarin interaction study that demonstrated no interaction of multiple 80 mg doses of febuxostat with warfarin. The Applicant also submitted the results of an in vitro study on induction potential on primary human hepatocytes. That study showed low potential to induce the 5 isoforms of cytochrome P450 studied.

The Clinical Pharmacology review team has requested, and the Applicant has agreed to conduct, a postmarketing study of the interaction between febuxostat and theophylline. Until that study is carried out the ULORIC label will contain a contraindication for the concomitant use of theophylline.

I am in agreement with the recommendations of the Clinical Pharmacology review team.

6. Clinical/Statistical

6.1. General Discussion

In the previous two review cycles the Applicant submitted the results of a Phase 2 dose-finding study and of two Phase 3 randomized, controlled trials of safety and efficacy. The Phase 3 trials demonstrated the efficacy of febuxostat 80 mg and 120 mg in reducing serum urate levels in patients with gout. However, the Phase 3 trials also showed a higher rate of cardiovascular thromboembolic events in patients receiving febuxostat than in controls. Because of the cardiovascular safety signal the Agency issued an Approvable letter that stated that additional data were needed to establish the cardiovascular safety of

febuxostat. The Approvable letter also suggested the Applicant study safety and efficacy of a lower dose.

The current submission contains the results of an additional randomized, active-controlled Phase 3 trial that compared febuxostat 40 mg and 80 mg to allopurinol. This new trial was several-fold larger than the previous Phase 3 studies. The new study confirmed the efficacy of the 80 mg dose and demonstrated efficacy of the 40 mg dose. No cardiovascular safety signal was identified in the new study. However, the study was not adequately powered to exclude a moderate increase in the rate of cardiovascular events with febuxostat.

6.2. Efficacy

In previous review cycles the Agency has reviewed the results of a Phase 3, dose-finding study (Study TMX-004) and two Phase 3 trials (Studies C02-009 and C02-010). Those studies showed the efficacy of febuxostat 80 mg in reducing serum urate levels and its superiority to allopurinol in doses typically used in clinical practice (Table 1; this and all other tables and figures copied from the clinical review of Dr. Jane Gilbert).

Table 1: Proportion of patients with sUA <6 mg/dL at final visit

Efficacy: Proportion with sUA<6 mg/dL at Final Visit				
Study	**Febuxostat 40 mg**	**Febuxostat 80 mg**	**Allopurinol 300 mg**	**Placebo**
F-153	45% ‡ (342/757)	67% * (507/756)	42% (318/755)	N/A
C02-009	N/A	72%* (183/253)	39% (102/263)	1% (1/127)
C02-010	N/A	74%* (185/249)	36% (88/242)	N/A
TMX - 004	56% (19/34)	76% (28/37)	N/A	0% (0/35)

Source: Complete Response to August 2006 Approvable Letter

* Indicates statistical significance versus allopurinol at p<0.001.

‡ Noninferior to allopurinol using the lower bound of the 95% confidence interval of the difference (-1.9%) being greater thanthe critical value of -10%.

The new Phase 3 clinical trial, Study F-GT06-153 (hereafter called Study F-153), was a 6-month, randomized, active-controlled study of safety and efficacy of febuxostat 40 mg and 80 mg in comparison with allopurinol in patients with gout and hyperuricemia. Allopurinol was given at the recommended starting dose of 300 mg daily in patients with normal renal function and 200 mg daily in patients with renal impairment. Randomization was stratified by renal function (normal vs. mild/moderate renal impairment). The primary endpoint for the study was the proportion of patients with a sUA of less than 6 mg/dL at the final study visit. For the comparison of febuxostat 80 mg to allopurinol a superiority test was utilized. Since febuxostat 40 mg was expected to be similar to allopurinol, but not superior, a non-inferiority analysis was specified to assess the efficacy of febuxostat 40 mg, utilizing a non-inferiority margin of 10%. This non-inferiority margin is reasonable given that the effect size of allopurinol has been demonstrated to be approximately 40% in prior studies. A non-inferiority margin of 10% would preserve at least three-quarters of the effect size of the active comparator, allopurinol.

Study F-153 enrolled 2269 subjects, the majority of whom (65%) had some degree of renal impairment. The baseline demographics were typical of the gout population, being predominantly male (approximately 95%) and of mean age approximately 52 years. Cardiovascular risk factors were common with a high mean body mass index (BMI, approximately 33 kg/m^2) indicating a high prevalence of obesity, high incidence of renal impairment, diabetes, hypercholesterolemia and hypertension. Approximately 80% of patients completed the 6 months of the study with similar proportions of dropouts in the various treatment arms. The rate of dropout due to adverse events or to lack of efficacy was not higher in the febuxostat arms than in the allopurinol arm.

Table 2: Baseline demographics, Study F-153

Variable	Treatment Group n (%)			
	Febuxostat 40 mg QD (N=757)	Febuxostat 80 mg QD (N=756)	Allopurinol 300/200 mg QD (N=756)	All Subjects (N=2269)
Gender				
Male	722 (95.4)	710 (93.9)	709 (93.8)	2141 (94.4)
Female	35 (4.6)	46 (6.1)	47 (6.2)	128 (5.6)
Race				
American Indian or Alaska Native	6 (0.8)	10 (1.3)	6 (0.8)	22 (1.0)
Asian	26 (3.4)	25 (3.3)	37 (4.9)	88 (3.9)
Black or African American	83 (11.0)	78 (10.3)	67 (8.9)	228 (10.0)
Native Hawaiian or Other Pacific Islander	11 (1.5)	10 (1.3)	11 (1.5)	32 (1.4)
White	620 (81.9)	618 (81.7)	625 (82.7)	1863 (82.1)
Other	11 (1.5)	15 (2.0)	8 (1.1)	34 (1.5)
Missing	0	0	2 (0.3)	2 (0.1)
Ethnicity				
Hispanic or Latino	47 (6.2)	49 (6.5)	53 (7.0)	149 (6.6)
Not Hispanic or Latino	710 (93.8)	707 (93.5)	702 (92.9)	2119 (93.4)
Missing	0	0	1 (0.1)	1 (0.0)
Age (yr)				
Mean ± SD	52.5±11.68	53.0±11.79	52.9±11.73	52.8±11.73
Range	21-85	21-85	19-85	19-85
Weight (lb)				
Mean ± SD	229.9±48.58	227.3±47.70	225.5±46.09	227.6±47.48
Range	117-449	102-474	102-425	102-474
Height (in)				
Mean ± SD	70.0±3.29	69.7±3.31	69.6±3.52	69.8±3.31
Range	56-80	60-79	56-80	56-80
Body Mass Index (kg/m²)				
Mean ± SD	32.9±6.37	32.9±6.39	32.7±6.23	32.8±6.33
Range	20-64	16-64	17-61	16-64
Baseline Serum Urate (mg/dL)				
Mean ± SD	9.6±1.15	9.6±1.20	9.5±1.19	9.6±1.18
Range	8-14	8-15	8-15	8-15
Completed Previous Febuxostat Study				
TMX-01-005/C02-021	98 (12.9)	88 (11.6)	90 (11.9)	276 (12.2)
Medical History				
Renal Function Moderately Impaired[a]	130 (17.2)	136 (18.0)	136 (18.0)	402 (17.7)
Renal Function Mildly Impaired[b]	349 (46.1)	367 (48.5)	365 (48.3)	1081 (47.6)
Renal Function Normal[c]	278 (36.7)	253 (33.5)	255 (33.7)	786 (34.6)
Kidney Stone	104 (13.7)	121 (16.0)	104 (13.8)	329 (14.5)
Diabetes	89 (11.8)	113 (14.9)	110 (14.6)	312 (13.8)
Hypercholesterolemia	52 (6.9)	53 (7.0)	57 (7.5)	162 (7.1)
Hyperlipidemia	299 (39.5)	308 (40.7)	335 (44.3)	942 (41.5)
Hypertension	388 (51.3)	402 (53.2)	409 (54.1)	1199 (52.8)

a Moderately impaired: baseline estimated creatinine clearance (ECC) 30 mL/min to 59 mL/min.
b Mildly impaired: ECC 60 mL/min to 89 mL/min.
c Normal: ECC ≥90 mL/min.

Patients treated with febuxostat 80 mg daily in Study F-153 experienced a reduction in sUA to below 6.0 mg/dL more frequently than patients receiving allopurinol (Table 1), confirming efficacy of the 80 mg dose seen in the previous studies. Febuxostat 40 mg was shown to be statistically non-inferior to allopurinol. In the prespecified subgroup of patients with renal impairment febuxostat 40 mg was shown to superior to allopurinol (50% vs. 42%). Among patients with a baseline serum urate of 10 mg/dL or higher a higher proportion of subjects achieved a serum urate of 6 mg/dL or less among patients receiving the febuxostat 80 mg dose that among those receiving the 40 mg dose (49% vs. 27%, Table 3).

Table 3: Proportion of subjects in Study F-153, by level of serum urate, who met the primary endpoint of a sUA < 6 mg/dL

	All subjects	sUA<10 mg/dL	sUA≥10 mg/dL
Allopurinol	**42%** *n=756*	**47%** *n=526*	**31%** *n=230*
Febuxostat 40 mg	**45%** *n=757*	**54%** *n=508*	**27%** *n=249*
Febuxostat 80 mg	**67%** *n=756*	**76%** *n=502*	**49%** *n=254*

Source: Takeda, Arthritis Advisory Committee Meeting, 11/24/2008.

6.2.1. Discussion of primary and secondary reviewers' comments and conclusions

The primary clinical reviewer, Dr. Jane Gilbert, concluded that the clinical trials had demonstrated efficacy of the 80 mg febuxostat dose and that this dose had also shown superiority to allopurinol. Dr. Gilbert concluded that the 40 mg febuxostat dose had demonstrated efficacy based on non-inferiority to allopurinol. In the subgroup of patients with renal impairment both the 80 mg and the 40 mg febuxostat group had demonstrated superiority to allopurinol. Dr. Joan Buenconsejo, the biostatistics reviewer, concluded that both the febuxostat 80 mg and the 40 mg doses had shown efficacy in lowering serum urate levels in patients with gout. I concur with the conclusions of Drs. Gilbert and Buenconsejo concerning the efficacy of febuxostat.

6.3. Safety

At the time of the second cycle review, the clinical review team concluded that there was an apparent cardiovascular safety signal. They identified no other safety signals that would preclude an approval.

The evidence indicating a cardiovascular safety signal consisted of a higher rate of cardiovascular deaths and SAEs in the febuxostat group compared to the control group. Overall, there were 4 deaths in the pooled febuxostat group in the randomized trials compared to none in controls (Table 4). The ratio of deaths in the febuxostat group compared to control exceeds the expected ratio of approximately 2:1 based on the exposure in the febuxostat group, which was approximately twice that in the control group (671 vs. 334 patient years). In the long-term extension studies, there were 8 additional deaths, all in the febuxostat group. The mortality rate among febuxostat-treated patients did not rise with longer duration of treatment. In fact the mortality rate was lower in long-term extensions studies than in the randomized controlled studies (0.38 vs. 0.60 events/100 pt-yrs). It is difficult to reach conclusions about the relationship of the deaths in the long-term extension studies to febuxostat treatment since these studies lacked a control group of adequate size (only 145 pt-yrs with control compared to 2121 pt-yrs with febuxostat).

Table 4: All-cause mortality in febuxostat clinical program by patient-years of exposure with data as of 08 February 2006

Treatment	Patient-Years of Exposure	Number of Deaths	Rate Per 100 Patient-Years	95% Confidence Interval
Phase 3 Randomized Controlled Studies				
Febuxostat Total	671	4	0.60	0.162-1.526
Allopurinol 300/100 mg QD	334	0	0.0	0.000-1.105
Long-Term Extension Studies				
Febuxostat Total	2121	8	0.38	0.163-0.743
Allopurinol 300/100 mg QD	145	0	0.0	0.000-2.538
Phase 3 Randomized Controlled and Long-Term Extension Studies				
Febuxostat Total	2792	12	0.43	0.222-0.751
Allopurinol 300/100 mg QD	479	0	0.0	0.000-0.770

Note: No subjects died in the Phase 1 studies or during treatment in the Phase 2 controlled clinical trial (TMX-00-004).
The confidence intervals are calculated based on Poisson distribution.

Source: FDA Clinical Review, July 2006

Investigation of the causes of death in the febuxostat group determined that most were cardiovascular in nature (Table 5). In order to further evaluate the cardiovascular safety of febuxostat the Applicant reviewed cardiovascular SAEs in a post hoc fashion. The Applicant classified thromboembolic cardiovascular SAEs according to Anti-Platelet Trialists Consortium (APTC) criteria. Primary APTC events were specified as cardiovascular deaths, non-fatal MIs, non-fatal stroke and non-fatal cardiac arrests. As shown in Table 6, the rate of investigator-reported primary APTC events was higher in the febuxostat group (0.8%) than in controls (0.2%). The major types of events were cardiovascular deaths and non-fatal MIs. The data do not show clear evidence of a dose response.

Table 5: Updated cardiovascular deaths in combined Phase 3 randomized controlled and long-term extension studies with data as of 08 February 2006

	Treatment						
	Placebo	Febuxostat					Allopurinol
Number of CV	(N=134) (PY=59.9)	Total (N=1692) (PY=2791.8)	40 mg (N=12) (PY=34.6)	80 mg (N=1221) (PY=1697.1)	120 mg (N=909) (PY=1006.1)	240 mg (N=134) (PY=54.0)	300/100 (N=642) (PY=479.1)
Deaths	0	9	0	5	4	0	0
Per 100 PY	0	0.32	0	0.29	0.40	0	0
95%CI[a]	(0–6.16)	(0.147-0.612)	(0–10.67)	(0.096-0.688)	(0.108-1.02)	(0–6.83)	(0-0.77)

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

a 95% CI were calculated based on Poisson distribution.

Source: FDA Clinical Review, July 2006

Table 6: Investigator-reported primary APTC events in randomized controlled trials, N (%)

Primary APTC Events	*Placebo*	*Febuxostat*				*Allopurinol*
		Total	80 mg	120 mg	240 mg	300/100 mg
	N=134	N=1177	N=523	N=520	N=134	N=521
Overall	**0**	**9 (0.8)**	**4 (0.8)**	**5 (1.0)**	**0**	**1 (0.2)**
CV Death	0	3 (0.3)	2 (0.4)	1 (0.2)	0	0
Non-fatal MI	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

Source: Complete Response to October 14, 2005 Approvable Letter

The Applicant also conducted a post hoc adjudication of APTC events by submitting potential cardiovascular events to blinded review by a single cardiologist, Dr. William White. This analysis showed similar results to the analysis of investigator-reported APTC events with a higher rate of adjudicated APTC events in the febuxostat group than in controls (0.59 vs. 0.19%). The 7 adjudicated events consisted of cardiovascular deaths and non-fatal MIs. The rate of APTC events was not increased in patients receiving febuxostat 120 mg as compared to those receiving 80 mg daily.

Table 7: Percentages of subjects with treatment-emergent adjudicated APTC events in the Phase 3 randomized controlled studies

	Treatment Group					
	Placebo	Febuxostat				Allopurinol
		Total	80 mg QD	120 mg QD	240 mg QD	300/100 mg QD
	(N=134)	(N=1177)	(N=523)	(N=520)	(N=134)	(N=521)
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

Source: Complete Response to October 14, 2005 Approvable Letter , p. 39.

Analysis of the data available at the time of the second cycle suggested a possible cardiovascular safety signal with febuxostat. However, the data were not conclusive for several reasons. First, cardiovascular thromboembolic events are expected events in this patient population given that many of the patients in the febuxostat studies had underlying cardiovascular risk factors, including prior cardiac history, hypertension, obesity and hyperlipidemia. In addition, gout itself has been shown to increase the risk of cardiovascular events. Second, the number of cardiovascular events was small, particularly in the control group (a single adjudicated APTC event among 521 subjects), such that the confidence intervals around the rates were wide and broadly overlapping between febuxostat and control groups, consistent with either an increased risk or a decreased risk with febuxostat. Third, there is no good physiologic rationale to explain an increased cardiovascular risk given that febuxostat decreases activity of xanthine oxidase and decreases serum uric acid and considering that elevated activity of xanthine oxidase and elevated serum uric acid have both been associated with increased cardiovascular risk. Nonclinical studies in animals also showed no evidence of cardiac toxicity. Finally, if febuxostat were truly associated with an increased risk of cardiovascular risk we might expect to have seen increased cardiovascular risk with increasing doses of febuxostat and with increasing duration of exposure, neither of which were observed in the clinical trials. Nonetheless, the higher rate of cardiovascular events in the febuxostat group compared to the control group is of clear concern. Additional information was necessary to evaluate the cardiovascular safety of febuxostat.

To further address the cardiovascular safety of febuxostat the Applicant conducted Study F-153. As noted above, Study F-153 was a randomized, double-blind, active controlled study of 2269 subjects randomized 1:1:1 to febuxostat 40 mg or 80 mg or allopurinol.

The number randomized to the allopurinol arm was approximately 3-times larger than the prior Phase 3 trials and the total size of the study was larger than the two prior Phase 3 studies combined. Approximately 1300 patients had cardiovascular risk factors. The protocol included a prespecified method for categorizing cardiovascular thromboembolic events by APTC criteria and a 3-member adjudication committee.

As shown in Table 8, 5 deaths occurred during the course of Study F-153: 3 in the allopurinol arm and 1 each in the two febuxostat arms. Thus, the rate of mortality was not increased in febuxostat-treated patients. When deaths due to cardiovascular events were analyzed, a similar pattern was observed (Table 9). A total of 2 cardiovascular deaths were observed in the allopurinol group (0.3%) as compared to none in the febuxostat group. Of note, the rate of mortality in the allopurinol group was similar to what had been observed in febuxostat-treated patients in the previous Phase 3 trials. Thus, cardiovascular mortality was not increased in the febuxostat arms compared to allopurinol-treated patients.

Table 8: Analyses of all mortality, Study F-153

Variable	Febuxostat 40 mg QD (N=757) (PY=343.5)	Febuxostat 80 mg QD (N=756) (PY=332.1)	Allopurinol 300/200 mg QD (N=756) (PY=337.9)
Number of Subjects with events	1	1	3
Rate (%)	0.13	0.13	0.40
95% Confidence Interval (%) +	(0.003, 0.734)	(0.003, 0.735)	(0.082, 1.155)
Fisher's exact test p-value			
Versus Allopurinol 300/200 mg QD	0.374	0.625	
Versus Febuxostat 40 mg QD		>0.999	
Relative Risk (95% CI) $			
Versus Allopurinol 300/200 mg QD	0.33 (0.03, 3.19)	0.33 (0.03, 3.20)	
Versus Febuxostat 80 mg QD	1.00 (0.06, 15.94)		
Rate per 100 patient-years	0.29	0.30	0.89
95% Confidence Interval @	(0.007, 1.622)	(0.008, 1.678)	(0.183, 2.594)

& Distributed as: allopurinol 200 mg (N=145) plus allopurinol 300 mg (N=611).
$ Continuity correction of 0.5 was used if either treatment group had 0 death events.
+ Exact confidence interval based on Binomial Distribution.
@ Exact confidence interval based on Poisson Distribution.
In column headings, N = number of subjects dosed; PY = total patient-years of exposure.

Source: Clinical Study Report, F-GT06-153, p. 230

Table 9: Cardiovascular mortality: previous RCTs compared with F-153

	Febuxostat-treated patients	Allopurinol-treated patients
Previous RCTs**		
N	1177	521
Number/% with CV Mortality by MedDRA preferred term	3/ .3%	0
F-GT06-153		
N	1513	755
Number/% with CV Mortality by MedDRA preferred term	0	2/ .3%
** C0-009 and C0-010; Cross-reference tables 8 and 18.		

The rate of adjudicated APTC events in Study F-153 (Table 10) was similar in the febuxostat 80 mg group as in the allopurinol group (0.4%) while the rate in the febuxostat 40 mg group was lower (0%). To determine what degree of cardiovascular risk Study F-153 could exclude a relative risk was calculated. As shown in **Table 11**, the relative risk of APTC events for the febuxostat 40 mg and 80 mg doses were 0.1 and 1, respectively reflecting the observation of a similar or lower rate of events. However, the upper bounds of the 95% confidence interval for the relative risk for these doses were 2.76 and 4.9, respectively, indicating that the study could not exclude an increased cardiovascular risk with febuxostat.

Table 10: Analysis of adjudicated APTC cardiovascular adverse events (Study F-153)

Variable	Treatment Group n (%)		
	Febuxostat 40 mg QD (N=757)	Febuxostat 80 mg QD (N=756)	Allopurinol 300/200 mg QD (N=756)
All APTC Events			
Number of subjects with events	0	3	3
Rate (%)	0.00	0.40	0.40
95% Confidence Interval (%)[a]	(0.000, 0.486)	(0.082, 1.155)	(0.082, 1.155)
Fisher's exact test p-value			
Versus Allopurinol 300/200 mg QD	0.125	>0.999	
Versus Febuxostat 40 mg QD		0.125	
Relative Risk (95% CI)[b]			
Versus Allopurinol 300/200 mg QD	0.14 (0.01, 2.76)	1.00 (0.20, 4.94)	
Versus Febuxostat 80 mg QD	0.14 (0.01, 2.76)		
APTC Events Summarized by Criterion			
Cardiovascular Death	0	0	2 (0.26)
Nonfatal Myocardial Infarction	0	1 (0.13)	1 (0.13)
Nonfatal Stroke	0	2 (0.26)	0

CI=confidence interval; N=number of subjects dosed; QD=once daily.
a Exact confidence interval based on Binomial Distribution.
b Continuity correction of 0.5 was used if either treatment group had zero APTC events.
Source: Clinical Study Report, F-GT06-153, p. 168.

Table 11: Relative risk (RR) with 95% confidence intervals (CI) for adjudicated APTC events

	F-40	F-80	F-120	F-240	Total: Febuxostat treated
N	757	1279	520	134	2690
C02-009					
RR		3.01	2.99	2.00	2.00
CI		(0.1, 73.6)	(0.1,73.1)	(0.04, 100.1)	(0.1, 41.6)
C02-010					
RR		2.96	2.02		2.5
CI		(0.3, 28.3)	(0.2, 2.1)		(0.3, 21.2)
F-GTO6-153					
RR	0.1	1			0.5
CI	(0.01, 2.76)	(0.2, 4.9)			(0.1, 2.5)
All Phase 3					
RR	0.2	1.75	1.8	1.06	1.19
CI	(0, 3.5)	(0.5, 5.95)	(0.4, 8.2)	(0.1, 19.5)	(0.4, 3.8)

Source: Response to FDA Information Request of 25 August 2008

The review division consulted the Division of Cardiovascular and Renal Products (DCRP), asking them to review the cardiovascular SAEs and provide an assessment of the cardiovascular safety of febuxostat. The DCRP consult examined the cardiovascular SAEs and stated that they did not see a pattern to indicate an increased cardiovascular risk with febuxostat. They did not recommend that further studies of cardiovascular risk with febuxostat be undertaken.

6.3.1. Discussion of primary reviewer's comments and conclusions

Dr. Gilbert concluded that the data from the first two Phase 3 trials suggested a cardiovascular safety signal based on the higher rate of overall mortality, cardiovascular mortality and cardiovascular SAEs. However, she also noted that there was significant uncertainty about any conclusions concerning cardiovascular risk with febuxostat due to the fact that the findings were based on small numbers of events with broad confidence intervals around the rates that were consistent with either increased or decreased risk. Dr. Gilbert noted that Study F-153 did not show a higher rate of cardiovascular events with febuxostat than with allopurinol. However, she also noted that Study F-153 contained relatively few cardiovascular events raising uncertainty about how well this study could exclude a cardiovascular risk with febuxostat. Dr. Gilbert concluded that while questions remain about the cardiovascular safety of febuxostat no cardiovascular risk was demonstrated in the new study. Given that there is a need for new, effective treatments

for gout she concluded that the risk-benefit profile for febuxostat is favorable and that it should be approved. I concur with her assessment.

7. Advisory Committee Meeting

The Arthritis Advisory Committee met on November 24, 2008 to discuss the safety and efficacy of febuxostat. The committee was concerned about the possibility of increased cardiovascular risk with febuxostat. The committee members discussed the need for new treatments for hyperuricemia in patients with gout in view of the large numbers of patients who are intolerant of currently available therapies or are inadequately treated. They recommended approval of febuxostat with a vote of 12-0 with 1 abstention. There was general agreement of the need for collecting additional information post-approval. However, there was not consensus on whether there should be a cardiovascular outcome study or whether an observational study would be adequate.

8. Labeling

8.1. Physician labeling

At the time of completion of this CDTL memo, detailed consideration of the label was ongoing. In view of the uncertainties regarding a possible cardiovascular safety signal with febuxostat the label

Regarding dosing, febuxostat should be given in the lowest dose that is effective at reducing serum urate to target levels of below 6.0 mg/dL.

b(4)

Febuxostat should be started at a dose of 40 mg daily in patients

9. DSI audits

Due to an unfortunate delay in conveying the consult request to DSI the study site inspections have not been completed at the time of writing of this CDTL memo.

10. Conclusions and recommendations

10.1. Regulatory action

Data from three adequate and controlled Phase 3 trials support the efficacy of febuxostat in lowering serum urate levels in patients with gout. In these three trials between 67% and 74% of patients achieved the target serum urate level of 6.0 mg/dL or below with the 80 mg daily dose. The results were statistically significant. They are also clinically meaningful since reduction of serum urate levels to below 6.0 mg/dL has been associated with resorption of tophi and reduced frequency of gout attacks. The efficacy of the febuxostat 40 mg dose was demonstrated in Study F-153 based on statistical non-

inferiority to allopurinol. Febuxostat was demonstrated efficacious in patients with higher serum urate levels (10 mg/dL and greater) and in patients with mild or moderate renal insufficiency, two subgroups of patients who are more refractory to current therapies. In the subgroup of patients with renal insufficiency febuxostat 40 mg was superior to a regimen of allopurinol that is typically used in clinical practice.

In the previous review cycle data from the two initial Phase 3 trials demonstrated an apparent cardiovascular thromboembolic safety signal but no safety concerns that would preclude an approval. In those trials there was a higher rate of cardiovascular death and cardiovascular serious adverse events. However, there was considerable uncertainty about whether the cardiac safety signal was real given the lack of a physiologic rationale and the small number of events involved. Because of the small number of events the confidence intervals around the rates were wide and overlapping, consistent with either an increased or a decreased rate of cardiovascular events. Subsequently, a third Phase 3 trial was conducted that did not show a cardiovascular safety signal. The results from this third study are reassuring in that this trial was much larger than the previous studies and enrolled a similar patient population, including a large proportion of patients with risk factors for cardiovascular events. However, some uncertainty remains about the cardiac safety of febuxostat since the third trial had only very small numbers of cardiovascular thromboembolic events.

In view of the clear evidence of efficacy of febuxostat, including efficacy in subgroups of patients who have inadequate treatment options available at present, and the evidence from Study F-153 that did not show a cardiovascular safety signal compared to allopurinol the risk-benefit relationship for febuxostat is favorable. So long as the DSI inspections do not show serious deficiencies in the conduct of Study F-153 and a solution can be found concerning the issue of the lack of a designated site for future manufacture of drug substance, febuxostat should be approved for the treatment of hyperuricemia in patients with gout. However, a cardiovascular outcome study should be required to gain more definite evidence concerning the cardiac safety of febuxostat.

10.2. Safety concerns to be followed postmarketing

The major safety concern that should be followed postmarketing is the risk of cardiovascular thromboembolic events. However, it is unclear that routine pharmacovigilance will provide new information about the cardiac safety of febuxostat even if febuxostat treatment is, in fact, associated with a moderate increase in the rate of cardiovascular events since these types events are not rare in this patient population and are, therefore, expected.

10.3. Risk Evaluation and Mitigation Strategy (REMS)

10.3.1. General considerations on the need for, and goals of, any REMS beyond standard labeling and pharmacovigilance

While there are still questions concerning the cardiac safety of febuxostat based on findings from the first two Phase 3 studies the third, much larger study did not show a

cardiac safety signal. The evidence for a safety signal is not strong and statistically the confidence intervals for the rate of cardiovascular events was consistent with either an increased or a decreased rate of cardiac events. Thus, a REMS is not warranted at the current time. The possible risks can be adequately conveyed through standard labeling and pharmacovigilance.

10.4. Postmarketing studies

10.4.1. Required studies

In view of the remaining questions about the cardiovascular safety of febuxostat the applicant should be required to conduct a study to provide more definite information about the risk of cardiovascular events. Since cardiovascular thromboembolic events are not uncommon in the patient population that will take febuxostat it is not clear that an observational study will be able to provide useful information. Therefore, a randomized cardiovascular outcome study should be conducted that is large enough and long enough to provide definitive information about the rate of cardiovascular events. In particular the trial must accrue a sufficient number of events to assess whether there is a moderate increase in the risk of cardiovascular events with febuxostat. The design of the trial should take into account the serious challenges in conducting such a study, including the likelihood that large numbers of patients in the control arm will cross over to the febuxostat arm because of inadequate control of serum urate levels.

The clinical reviewer, Dr. Jane Gilbert, concluded that the Applicant should be required to conduct both a cardiovascular outcome study and an observational study. She reasoned that an observational study would have the benefits of simplicity of initiation and earlier availability of data. She also noted that an observational study could enroll patients who had failed or were intolerant of allopurinol. While I agree that an observational study would be easy to initiate I am not convinced that a trial lacking a randomized control arm would be able to provide information relevant to the key question under consideration, namely whether treatment with febuxostat is associated with a moderate increase in cardiovascular risk. Therefore, I do not agree that an observational study should be required.

10.4.2. Commitments (PMCs)

No additional clinical PMC's are necessary. The Applicant should commit to conducting a postmarketing study of the interaction between febuxostat and theophylline.

10.4.3. Other agreements with Sponsor

None.

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/s/

Jeffrey N Siegel
1/2/2009 12:54:16 PM
MEDICAL OFFICER