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Testimony Before the FDA's Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee

Febuxostat Should Be Withdrawn From the Market

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I am Dr. Michael Carome, Director of Public Citizen's Health Research Group. Public Citizen and I have no financial conflicts of interest.

On June 21, 2018, Public Citizen petitioned the Food and Drug Administration (FDA) to immediately require the removal from the market of all medications containing febuxostat because (1) the drug increases the risk of death compared with alternative therapies and (2) there exist other effective medications that have been approved by the FDA for treatment of gout that have a lower risk of death.

We strongly urge the committee to recommend that the FDA grant our citizen petition.

FDA preapproval assessments of the initial new drug applications (NDAs) for febuxostat

First NDA Submission

Serious concerns about increased risks of adverse cardiovascular events and death predated the approval of febuxostat and resulted in the agency issuing complete response letters to the first two NDA submissions.

The sponsor submitted the initial NDA in December 2004 seeking approval for 80-milligram (mg) and 120-mg febuxostat tablets, dosed daily for treatment of hyperuricemia associated with gout. The company requested priority review, but that request was rejected because of insufficient evidence of "the superiority of febuxostat to existing therapy" and the existence of a "reasonably effective uric acid lowering treatment currently on the market."[1]

The initial NDA included efficacy and safety data from a 28-day dose-response phase 2 trial (TMX-00-004) and its long-term extension trial (FOCUS); and the phase 3 FACT and APEX trials and their long-term extension trial (EXCEL).[2] FACT was a double-blind, randomized trial comparing febuxostat at doses of 80 mg or 120 mg with allopurinol at a dose of 300 mg once daily for 52 weeks in 760 subjects with gout and hyperuricemia (serum uric acid [SUA]≥8 mg/deciliter

[1] Food and Drug Administration. Administrative and correspondence documents for NDA 21-856. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_AdminCorres_P2.pdf. Accessed January 8, 2019. PDF p. 53.
[2] Food and Drug Administration. Medical review for NDA 21-856. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_MedR_P2.pdf. Accessed January 8, 2019. PDF p. 92.

[dL]).[3] APEX was a double-blind, randomized trial comparing febuxostat (at doses of 80 mg, 120 mg, or 240 mg) with allopurinol (at doses of 300 mg or 100 mg depending on renal function) and with placebo once daily for 28 weeks in 1,072 subjects with gout and hyperuricemia (SUA≥8 mg/dL). The primary endpoint for both phase 3 trials was a surrogate marker: an SUA concentration below 6 mg/dL at each of the last three monthly measurements.

In their assessment of the initial submission, the FDA reviewers noted that eight deaths had occurred in febuxostat-group subjects in the phase 2 and 3 trials and the long-term EXCEL extension trial, including two deaths due to myocardial infarction, whereas no subject deaths occurred in the allopurinol and placebo comparator groups.[4] Most of the deaths occurred after 170 days of febuxostat exposure.[5] FDA reviewers also expressed significant concern about an excess of serious adverse cardiovascular events in febuxostat-group subjects (see Table 1).[6]

Table 1: Excerpts from FDA analysis of serious adverse events in review of initial NDA for febuxostat

Serious adverse events	Placebo (N=172)	Allopurinol (N=692)	Febuxostat (N=1,707)
Congestive heart failure	0	1	8
Ischemic coronary artery disease (ACS, acute MI, angina, MI)	0	2	17
Atrial fibrillation, supraventricular tachycardia	0	0	8
Cardiac arrest	0	0	2
Cerebral vascular accident, TIA	0	0	9

ACS: acute coronary syndrome; MI: myocardial infarction; TIA: transient ischemic attack

In terms of efficacy, FDA reviewers concluded that there was substantial evidence of efficacy to support the sponsor's proposed indication for febuxostat, treatment of hyperuricemia associated with gout).[7] However, the FDA reviewers noted that no trial had presented evidence of a reduction in gout flares, the most important clinical endpoint in gout treatment, for febuxostat compared with allopurinol or placebo.[8]

The lead FDA clinical reviewer concluded that "the risk/benefit analysis is not favorable for [febuxostat] at this time."[9] The FDA decided not to approve the NDA for febuxostat and in

[3] Becker MA, Schumacher HR, Wortmann RL, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. *N Engl J Med*. 2005;353(23):2450-2461.
[4] Food and Drug Administration. Medical review for NDA 21-856. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_MedR_P3.pdf. Accessed January 8, 2019. PDF pp. 1-2.
[5] *Ibid.* PDF p. 8.
[6] *Ibid.* PDF pp. 26-27.
[7] Food and Drug Administration. Medical review for NDA 21-856. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_MedR_P4.pdf. Accessed January 8, 2019. PDF p. 54.
[8] *Ibid.* PDF p. 86.
[9] *Ibid*. PDF p. 54.

October 2005 issued an approvable letter primarily because the application raised "concerns regarding the potential for [febuxostat] 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."[10]

Second NDA Submission

In February 2006, the sponsor re-submitted the NDA for approval of 80-mg and 120-mg once-daily febuxostat tablets for the same indication.[11] The resubmission included a reanalysis of the prior clinical trial data augmented by new safety data from the then-ongoing long-term extension clinical trials (FOCUS and EXCEL).[12]

FDA reviewers' analysis of the updated clinical safety data continued to raise concern that febuxostat increased the risk of all-cause mortality, cardiovascular mortality, and serious adverse cardiovascular events compared with exposure to allopurinol or placebo. Overall, there had been four deaths in randomized controlled trials and eight deaths in long-term extension studies among febuxostat-exposed subjects — including four additional deaths in the febuxostat arm from the long-term extension FOCUS trial (C02-021) — compared with no deaths among the allopurinol- and placebo-group subjects.[13] Nine of the 12 deaths among febuxostat-exposed subjects were attributable to cardiovascular causes, including five related to myocardial infarction.[14]

In a reanalysis of safety data categorizing adverse events according to Antiplatelet Trialists Collaboration (APTC) primary events (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and non-fatal cardiac arrest) and secondary events (angina, revascularization, transient ischemic attack, venous and peripheral arterial vascular thrombotic events, and non-fatal congestive heart failure), FDA reviewers noted a numerical excess of investigator-reported primary and secondary APTC events in febuxostat-exposed subjects. In the phase 3 randomized FACT and APEX trials, 0.9% of febuxostat-exposed subjects (10 of 1,177) had an investigator-reported treatment-emergent primary APTC event compared with only 0.2% of allopurinol-exposed subjects (1 of 521).[15]

The Director of the Division of Anesthesia, Analgesia and Rheumatology Products made the following comments in his summary review:

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[10] Food and Drug Administration. Approvable letter(s) for NDA 21-856. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_Approvable.pdf. Accessed January 8, 2019. PDF p. 6.
[11] Food and Drug Administration. Medical review for NDA 21-856. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_MedR_P1.pdf. Accessed January 8, 2019. PDF p. 84.
[12] *Ibid*. PDF pp. 89-90.
[13] *Ibid*. PDF p. 91.
[14] *Ibid*. PDF pp. 95-96.
[15] Food and Drug Administration. Medical Review for NDA 21-856. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_MedR_P2.pdf. Accessed January 8, 2019. PDF p. 11.

> This complete response does not adequately address the cardiovascular safety concerns noted during the first review cycle for the application. … I am convinced by the review team's assessment that a clear signal of risk remains, even in the most cautious analysis. ... [T]he apparent increase in cardiovascular thromboembolic adverse events in the [febuxostat]-exposed subject population results in my continued concern that the risks associated with this product may outweigh the benefits. **This is especially a concern for a product where the approval would be based on a surrogate (uric acid reduction), not on an outcome assessment. To approve a drug on such a surrogate when an unresolved signal of potential, serious adverse [cardiovascular] effects is outstanding does not appear warranted.**[16] [Emphasis added]

Therefore, the FDA again appropriately denied approval of febuxostat and issued a second approvable letter in August 2006 that required "further data to clarify the cardiovascular risks of the proposed doses and/or provide data on the safety and efficacy of lower doses of febuxostat in order to assure us that a dose level(s) with favorable risk-benefit characteristics has been defined."[17]

Third NDA submission

In June 2008, the sponsor resubmitted the NDA for febuxostat. In response to the FDA's ongoing concerns regarding the cardiovascular safety of febuxostat, the sponsor undertook the CONFIRMS trial, a double-blind, randomized trial that compared febuxostat (40 mg or 80 mg) with allopurinol dosed daily over six months in subjects with gout and hyperuricemia (SUA≥8 mg/dL).[18] The primary endpoint for the trial was the proportion of subjects in each trial group with an SUA concentration below 6 mg/dL at the final study visit. The CONFIRM trial enrolled 2,269 subjects.

Results of the CONFIRMS trial showed that febuxostat 40 mg was non-inferior to allopurinol in achieving the primary endpoint (45.2% vs. 42.1%, $p<0.001$), whereas febuxostat 80 mg daily achieved the primary endpoint in 67.1% of subjects, which was superior to both febuxostat 40 mg and allopurinol ($p<0.001$ for both comparisons).[19] However, the trial did not show any statistically significant differences in the proportion of subjects who experienced gout flares between the three groups during the trial.

In terms of safety, there were two deaths among the febuxostat-exposed subjects and three deaths among the allopurinol-exposed subjects.[20] Three subjects in the febuxostat 80-mg group and three

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[16] *Ibid*. PDF p. 81.
[17] Food and Drug Administration. Approvable letter(s) for NDA 21-856. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_Approvable.pdf. Accessed January 8, 2019. PDF p. 2.
[18] Becker MA, Schumacher HR, Espinoza LR, et al. The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: the CONFIRMS trial. *Arthritis Res Ther*. 2010;12(2):R63.
[19] *Ibid.*
[20] Food and Drug Administration. Medical review for NDA 21-856. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_MedR_P1.pdf. Accessed January 8, 2019. PDF p. 44.

subjects in the allopurinol group experienced adjudicated APTC events, whereas none in the febuxostat 40-mg group experienced such events.[21]

Although the CONFIRMS trial ultimately did not find the same safety signal for adverse cardiovascular events associated with febuxostat exposure compared with allopurinol exposure that had been seen in the earlier randomized trials, FDA reviewers noted that the upper bound of the 95% confidence intervals [CIs] for the relative risk of APTC events for the febuxostat 40-mg and 80-mg groups compared with the allopurinol group were 2.76 and 4.9, respectively, which indicated that the trial could not exclude an increased risk of adverse cardiovascular events with febuxostat.[22] Importantly, FDA reviewers concluded that the small number of adverse cardiovascular events in the CONFIRMS trial made "any results fragile and conclusions speculative at best."[23] Multiple FDA reviewers noted that questions and uncertainty remained about the cardiovascular safety of febuxostat based on the available data from the premarket clinical trials.[24,25,26]

In February 2009, the FDA approved febuxostat for the chronic management of hyperuricemia in patients with gout.[27] However, the FDA required that the sponsor perform a large randomized, controlled postmarket trial to determine whether the use of febuxostat is associated with a moderate increase in the risk of serious adverse cardiovascular outcomes as compared to allopurinol.[28]

Notably, approval of febuxostat might not have occurred without the ability of the FDA to mandate postmarketing clinical trials under the authority granted by the Food and Drug Administration Amendments Act of 2007 (FDAAA), a provision that took effect in March 2008.[29] Indeed, in his Summary Review, the Director of the FDA's Office of Drug Evaluation II stated that "had we not had the new authorities given under FDAAA[,] which gives me some confidence that we can dictate a study such that we can get a definitive answer, my conclusion on whether to

[21] *Ibid*. PDF p. 50.
[22] Food and Drug Administration. Cross discipline team leader review for NDA 21-856. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_CrossR.pdf. Accessed January 8, 2019. PDF p. 20.
[23] Food and Drug Administration. Office director memo for NDA 21-856. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_ODMemo.pdf. January 8, 2019. PDF p. 5.
[24] Food and Drug Administration. Medical review for NDA 21-856. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_MedR_P1.pdf. Accessed January 8, 2019. PDF p. 63.
[25] Food and Drug Administration. Cross discipline team leader review for NDA 21-856. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_CrossR.pdf. Accessed January 8, 2019. PDF p. 21.
[26] Food and Drug Administration. Statistical review for NDA 21-856. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_StatR_P1.pdf. Accessed January 8, 2019. PDF p. 6.
[27] Food and Drug Administration. Approval letter for NDA 21-856. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_Approv.pdf. Accessed January 8, 2019.
[28] *Ibid*. PDF p. 4.
[29] *Ibid*. PDF p. 3.

approve or not may have been different."[30] Likewise, because of concerns about cardiovascular safety, some members of the Arthritis Advisory Committee "were only willing to recommend approval due to the recent passage of FDAAA, which provides the Agency with regulatory authority to require studies and to implement strict time-lines for completion."[31]

Confirmatory evidence of harm from febuxostat

The Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidity (CARES) trial was a double-blind, randomized multicenter trial comparing once-daily febuxostat with once-daily allopurinol. Doses of both medications were titrated based on a goal serum uric acid level less than 6 mg/dL and based on renal function.[32]

From April 2010 through May 2017, the CARES trial investigators enrolled 6,190 subjects who had major cardiovascular disease before randomization (history of myocardial infarction, hospitalization for unstable angina, coronary or cerebral revascularization procedure, stroke, hospitalization for transient ischemic attack, peripheral vascular disease, or diabetes mellitus with evidence of microvascular or macrovascular disease), gout, and hyperuricemia (SUA≥7 mg/dL or ≥6 mg/dL if "inadequately controlled gout" after one-to-three week washout from previous gout therapies). Patients with severe renal impairment (eCLcr<30 mL/min) were excluded from the study.

The primary composite endpoint of the trial was the first occurrence of cardiovascular death, nonfatal stroke, nonfatal myocardial infarction, or urgent revascularization for unstable angina. The secondary safety endpoints included a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke, as well as the individual components of the primary endpoint. Death from any cause was one of several additional prespecified safety endpoints. The median duration of follow-up was 968 days for febuxostat-exposed subjects and 942 days for allopurinol-exposed subjects.

Premature discontinuation of trial medication was high in both the febuxostat-group subjects (57.3%) and the allopurinol-group subjects (55.9%), and the percentage of subjects who did not complete all trial visits was 45% for both groups. Importantly, such factors would be expected to bias towards the null hypothesis, underestimating the risk of febuxostat use.

There was no significant difference in the composite primary cardiovascular outcome (hazard ratio 1.03, 95% CI 0.87-1.23) (see Table 24 and Figure 5, excerpted from the FDA briefing document[33]).

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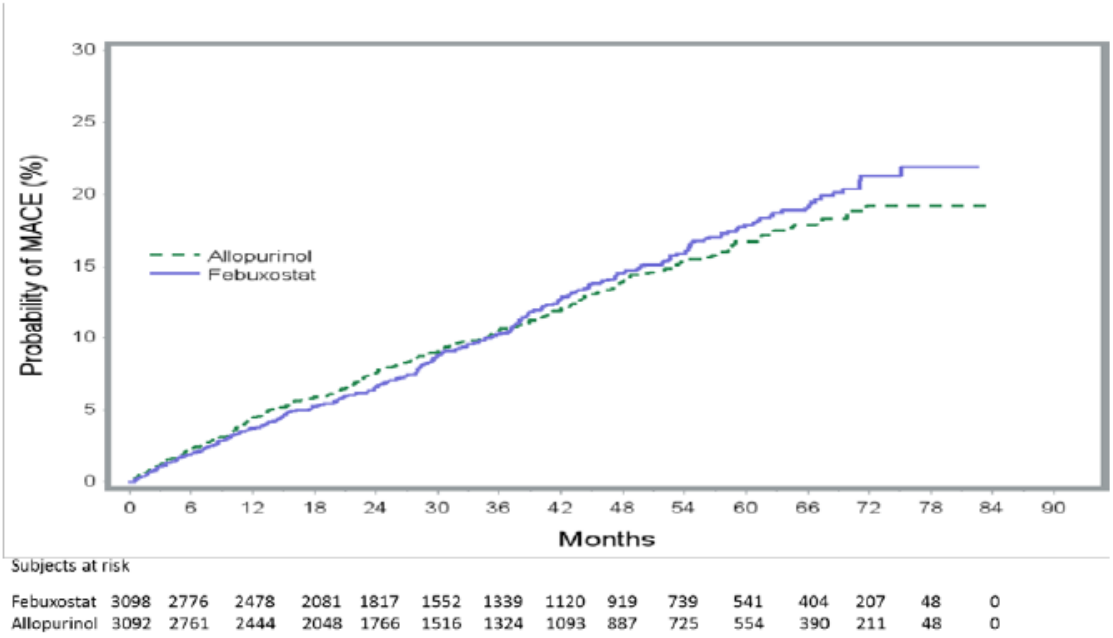
[30] Food and Drug Administration. Office director memo for NDA 21-856. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_ODMemo.pdf. Accessed January 8, 2019. PDF p. 7.
[31] Food and Drug Administration. Summary review for NDA 21-856. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_SumR.pdf. Accessed January. PDF p. 11.
[32] White WB, Saag KG, Becker MA, et al. Cardiovascular safety of febuxostat or allopurinol in patients with gout. *N Engl J Med*. 2018:1200-1210.
[33] Food and Drug Administration. FDA briefing document: Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee meeting. January 11, 2019.

Table 24 Primary Analysis of MACE – Number of Events

	Febuxostat N=3098 PY=8799.5	Allopurinol N=3092 PY=8675.7	Hazard Ratio* (95% CI)
MACE	335 [3.8]	321 [3.7]	1.03 (0.89, 1.21)
Cardiovascular death	134 [1.5]	100 [1.1]	1.34 (1.03, 1.73)
Non-fatal MI	111 [1.2]	118 [1.3]	0.93 (0.72, 1.21)
Non-fatal Stroke	71 [0.8]	70 [0.8]	1.01 (0.73, 1.41)
Unstable Angina with Urgent Coronary Revascularization	49 [0.5]	56 [0.6]	0.86 (0.59, 1.26)

*Hazard Ratio for Febuxostat vs. Allopurinol
PY=person-year until first MACE or trial discontinuation
[] indicates incidence rate per 100 person-years
Source: Created by the statistical reviewer

Figure 5. Kaplan-Meier Cumulative Probability of Primary MACE by Treatment



However, there were statistically significant differences in all-cause mortality and cardiovascular mortality between the two groups (see Table 25 and Figures 6 and 7 excerpted from the FDA briefing document[34]).

https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM629362.pdf. Accessed January 9, 2019. Page 60.
[34] *Ibid.* Pages 61-63.

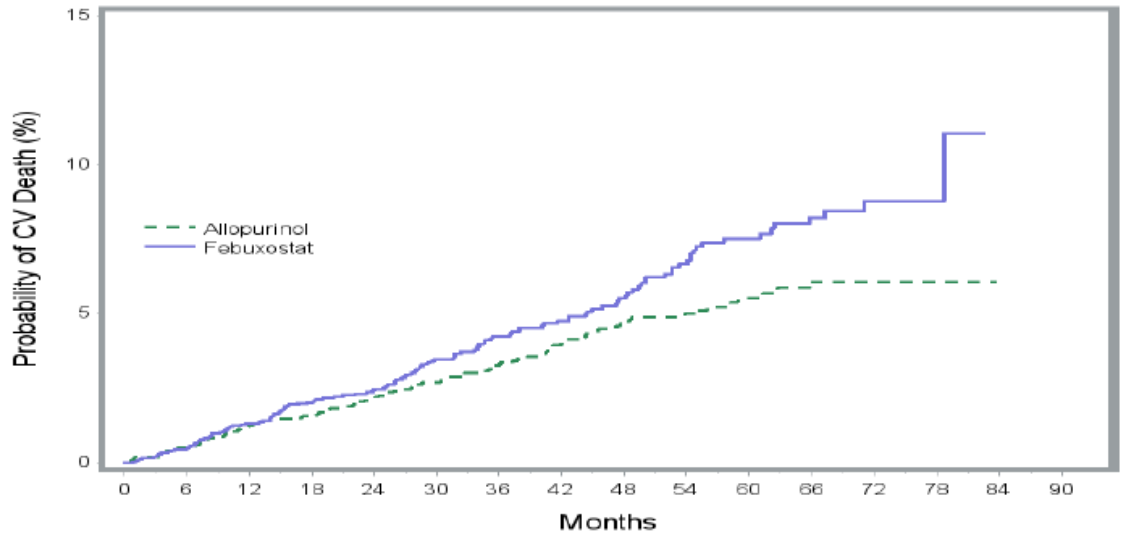
Table 25. Secondary Analysis of Cardiovascular Endpoints – Number of Events

	Febuxostat N=3098	Allopurinol N=3092	Hazard Ratio* (95% CI)
APTC	296 [3.3]	271 [3.1]	1.09 (0.92, 1.28)
All-Cause Death	243 [2.6]	199 [2.2]	1.22 (1.01, 1.47)
CV Death	134 [1.5]	100 [1.1]	1.34 (1.03, 1.73)
Non-CV Death	109 [1.2]	99 [1.1]	1.10 (0.84, 1.45)
All-Cause Death (on-Treatment)	36 [0.5]	27 [0.4]	1.31 (0.80, 2.16)

*Hazard Ratio for Febuxostat vs. Allopurinol
[] indicates incidence rate per 100 person-years
Source: Created by the statistical reviewer

During the trial, 243 (7.8%) of 3,098 subjects in the febuxostat group died, and 199 (6.4%) of 3,092 subjects in the allopurinol group died, which corresponded to a hazard ratio for all-cause mortality of 1.22 (95% CI 1.01-1.47; p=0.04). This difference in all-cause mortality rates was driven primarily by the difference in cardiovascular death: There were 134 cardiovascular deaths in the febuxostat group (4.3% of subjects) compared with 100 such deaths in the allopurinol group (3.2% of subjects), which corresponds to a hazard ratio for cardiovascular mortality of 1.34 (95% CI 1.03-1.73; p=0.03).

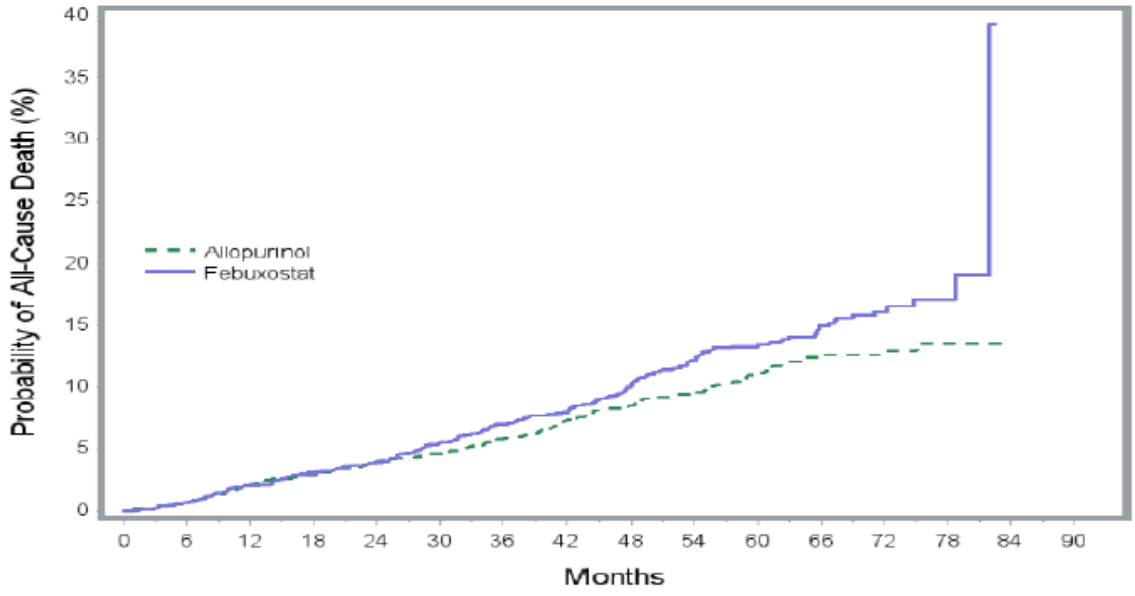
Figure 6. Kaplan-Meier Plot for Cardiovascular Death



Subjects at risk

Febuxostat	3098	2815	2535	2146	1888	1626	1410	1199	992	794	593	440	230	51	0
Allopurinol	3092	2804	2510	2119	1848	1589	1397	1165	962	797	609	434	235	57	0

Figure 7. Kaplan-Meier Plot for All-Cause Death



Subjects at risk

Febuxostat	3098	2820	2537	2153	1897	1634	1419	1209	998	798	597	441	232	51	0
Allopurinol	3092	2809	2520	2131	1856	1601	1410	1177	969	803	613	434	235	57	0

The most common cause of cardiovascular mortality was sudden cardiac death, which occurred in 83 febuxostat-treated subjects (2.7%) and 56 allopurinol-treated subjects (1.8%). The majority of the subject deaths (63%, 277 of 442) occurred more than 30 days after discontinuation of the trial drug. However, the trend towards excess cardiovascular and all-cause deaths in febuxostat-group subjects was seen when data were analyzed for each of the following overlapping timeframes: during trial drug exposure, during drug exposure or within 30 days of discontinuation of the trial drug, and for the total duration of follow-up. In a prespecified analysis of events that occurred during study drug exposure or within 30 days of discontinuation of the trial drug, the rate of cardiovascular death was higher in the febuxostat group than in the allopurinol group (hazard ratio 1.49; 95% CI 1.01-2.22; p=0.047). For this same timeframe, the rate of death from any cause also was nominally higher in the febuxostat group than in the allopurinol group, but this difference was not statistically significant (hazard ratio 1.26; 95% CI 0.93-1.72; p=0.14).

The FDA statistical reviewer also conducted a series of analyses of cardiovascular death and all-cause death by various time windows after discontinuation of the study drug (see Table 28 excerpted from the FDA briefing document[35]).

[35] *Ibid.* Page 65.

Table 28. Analysis of CV Death and All-Cause Death – Number of Events

	Febuxostat N=3098	Allopurinol N=3092	Hazard Ratio* (95% CI)
CV Death (on-study)	134	100	1.34 (1.03, 1.73)
CV Death (on-treatment)	23	14	1.62 (0.84, 3.16)
CV Death (on-treatment + 30 days)	62	41	1.49 (1.01, 2.22)
CV Death (on-treatment + 60 days)	76	53	1.42 (1.00, 2.01)
All-Cause Death (on-study)	243	199	1.22 (1.01, 1.47)
All-Cause Death (on-treatment)	36	27	1.31 (0.80, 2.16)
All-Cause Death (on-treatment + 30 days)	92	72	1.26 (0.93, 1.72)
All-Cause Death (on-treatment + 60 days)	119	96	1.22 (0.94, 1.60)

*Hazard Ratio for Febuxostat vs. Allopurinol
Source: Created by the statistical reviewer

Notably, the point estimates for all the hazard ratios are in the same direction and indicate that the finding of an increased risk of cardiovascular death with febuxostat compared with allopurinol is robust. In addition, a sensitivity analysis by final dose of treatment drug showed a higher rate of major adverse cardiovascular events (MACE), cardiovascular death, and all cause death in subjects whose final daily dose of febuxostat was 80 mg compared with those whose final dose was 40 mg, consistent with dose-related toxicity (see Table 29 excerpted from the FDA briefing document[36]).

[36] *Ibid.* Page 66.

Table 29. Sensitivity Analysis by Renal Function Status and Final Dose of Treatment Drug

	Febuxostat N=3092 % (n/N)		Allopurinol N=3090 % (n/N)				
	40 mg	80 mg	200 mg	300 mg	400 mg	500 mg	600 mg
MACE	9.6% (180/1884)	12.7% (154/1208)	11.6% (78/673)	8.7% (120/1379)	12.5% (97/778)	6.8% (9/132)	13.3% (17/128)
Normal	8.2% (13/159)	5.0% (4/80)	0/0	6.8 % (10/148)	2.5% (1/40)	6.7% (1/15)	20% (5/25)
Mild Impaired	7.3% (55/756)	11.9% (55/461)	0/4	7.1% (55/772)	7.6% (18/238)	6.1% (7/115)	11.8% (12/102)
Moderately Impaired	11.6% (112/969)	14.2% (95/667)	11.7% (78/669)	12.0% (55/459)	15.6% (78/500)	50.0% (1/2)	(0/1)
CV Death	3.6% (68/1884)	5.4% (65/1208)	3.1% (21/673)	1.5% (21/1379)	2.7% (21/778)	0.8% (1/132)	2.3% (3/128)
Normal	3.1% (5/159)	1.3% (1/80)	0/0	0.7% (1/148)	2.5% (1/40)	0/15	4.0% (1/25)
Mild Impaired	2.2% (17/756)	3.7% (17/461)	0/4	1.4% (11/772)	2.1% (5/238)	0.9% (1/115)	2.0% (2/102)
Moderately Impaired	4.7% (46/969)	7.0% (47/667)	3.1% (21/669)	4.6% (21/459)	7.2% (36/500)	0/2	0/1
All-Cause Death	6.5% (122/1884)	9.9% (120/1208)	6.5% (44/673)	5.3% (73/1379)	9.0% (70/778)	4.5% (6/132)	4.7% (6/128)
Normal	4.4% (7/159)	6.3% (5/80)	0/0	2.7% (4/148)	2.5% (1/40)	6.7% (1/15)	4.0% (1/25)
Mild Impaired	4.0% (30/756)	5.4% (25/461)	0/4	3.8% (29/772)	4.2% (10/238)	4.3% (5/115)	4.9% (5/102)
Moderately Impaired	8.8% (85/969)	13.5% (90/667)	6.6% (44/669)	8.7% (40/459)	11.8% (59/500)	0/2	0/1

*Renal function category was based on the baseline estimated creatinine clearance value; therefore, 8 subjects (6 with febuxostat and 2 with allopurinol) with missing value were excluded from this analysis. This resulted in missing one CV death event.

Source: Created by the statistical reviewer

Thus, the data from the CARES trial provide strong evidence confirming the earlier concerns that treatment with febuxostat carried an excess risk of fatal cardiovascular events.

Lack of clear meaningful clinical benefit with febuxostat over other gout therapy

In addition to evidence of febuxostat's unique risks of serious harm, there is no convincing evidence that febuxostat is more effective than other existing therapies for the prevention of clinically relevant outcomes for patients with gout. As discussed above, all phase 3 clinical trials in the febuxostat clinical program were designed to demonstrate febuxostat's ability to lower serum uric acid levels. However, the premarket trials and the large postmarket study found no advantage with use of febuxostat over use of allopurinol for preventing gout flares, and some trials demonstrated an increased risk of gout flares in febuxostat-exposed subjects compared with

allopurinol-exposed subjects.[37,38,39,40] There also is no evidence from the randomized clinical trials that use of febuxostat at 40-mg or 80-mg daily doses results in faster resolution of tophi than use of allopurinol (or placebo). A Cochrane Library systematic review article published in 2012 concluded there were no significant differences in effectiveness between febuxostat and allopurinol.[41]

Finally, the most striking findings in the FDA's analysis of allopurinol and febuxostat utilization from 2009-2016 were that the proportion of new users of allopurinol who switched to febuxostat was only 2.7%, whereas the proportion of new users of febuxostat who switched to allopurinol was 9.7%.[42]

Conclusions

In summary, there is substantial evidence that the serious cardiovascular harms of febuxostat outweigh any purported clinical benefit. Febuxostat, therefore, should immediately be withdrawn from the U.S. market to avoid further preventable harm to patients. Although initial clinical trials strongly suggested an increased cardiovascular risk with febuxostat and appropriately caused the FDA to repeatedly deny approval of the NDA for this medication, a later phase 3 randomized clinical trial of inadequate duration and power unfortunately provided temporary false hope that perhaps febuxostat was safe.

The results of the FDA-mandated postmarket trial provide additional high-quality evidence of a causal link between treatment with febuxostat and increased risk of all-cause death and cardiovascular death. The FDA almost certainly would have denied approval of febuxostat if data from this postmarket trial had been available at the time of the third NDA submission. Consistent with the precautionary principle of public health, we strongly urge the committee to recommend that the FDA grant our citizen petition and remove febuxostat from the market.

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