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

Febuxostat Should Be Removed From the Market

January 11, 2019

Michael Carome, M.D.
Public Citizen's Health Research Group

(I have no financial conflicts of interest)

Major Comment

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.

First NDA Submission

- 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."

First NDA Submission – Key Trials

- 28-day dose-response phase 2 trial (TMX-00-004) and its long-term extension trial (FOCUS)
- FACT: febuxostat (80 mg or 120 mg daily) vs allopurinol (300 mg daily) for 52 weeks in 760 subjects
- APEX: febuxostat (80 mg, 120 mg, or 240 mg) vs allopurinol (300 mg or 100 mg depending on renal function) or placebo for 28 weeks in 1,072 subjects
- EXCEL: long-term extension of FACT and APEX

First NDA Submission
Safety Concerns

- **8 deaths had occurred in febuxostat-group subjects in the phase 2 and 3 trials and the long-term EXCEL extension trial, including 2 deaths due to myocardial infarction, whereas no subject deaths occurred in the allopurinol and placebo comparator groups.**

First NDA Submission
Safety Concerns

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

First NDA Submission Efficacy Assessment

- 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).
- 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

First NDA Submission
Approval Rejected

- In October 2005, the FDA 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.”

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.
- 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).

Second NDA Submission
Unresolved Safety Concerns

- Overall, there had been 4 deaths in randomized controlled trials and 8 deaths in long-term extension studies among febuxostat-exposed subjects compared with no deaths among the allopurinol- and placebo-group subjects.
- In a reanalysis of safety data categorizing adverse events according to the Antiplatelet Trialists Collaboration (APTC), FDA reviewers noted a numerical excess of investigator-reported primary and secondary APTC events in febuxostat-exposed subjects.

Second NDA Submission Approval Rejected

- **Director of the Division of Anesthesia, Analgesia and Rheumatology Products: "*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.*" *[emphasis added]***

Second NDA Submission Approval Rejected

- 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.”

Third NDA Submission

- In June 2008, the sponsor re-submitted the NDA for approval of febuxostat for the same indication.
- 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 2,269 subjects with gout and hyperuricemia.

Third NDA Submission
Safety Assessment

- There were 2 deaths among the febuxostat-exposed subjects and 3 deaths among the allopurinol-exposed subjects in the CONFIRMS trial.
- FDA reviewers noted that the upper bound of the 95% confidence intervals (CI) 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.
- 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."

Third NDA Submission
FDA Approval

- In February 2009, the FDA approved febuxostat for the chronic management of hyperuricemia in patients with gout.
- 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.
- 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.

Third NDA Submission
FDA Approval

- 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 approve or not may have been different.
- 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."

CARES Trial: Confirmatory Evidence of Harm From Febuxostat

- **The CARES Trial**
  - Double-blind, randomized multicenter trial comparing once-daily febuxostat with once-daily allopurinol.
  - Enrolled 6,190 subjects who had major cardiovascular disease before randomization, gout, and hyperuricemia.
  - The primary composite endpoint of the trial was the first occurrence of CV death, nonfatal stroke, nonfatal MI, or urgent revascularization for unstable angina.
  - The secondary safety endpoints included a composite of CV death, nonfatal MI, 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.

CARES Trial: Confirmatory Evidence of Harm From Febuxostat

- **The CARES Trial**
  - **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.**

CARES Trial Results

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

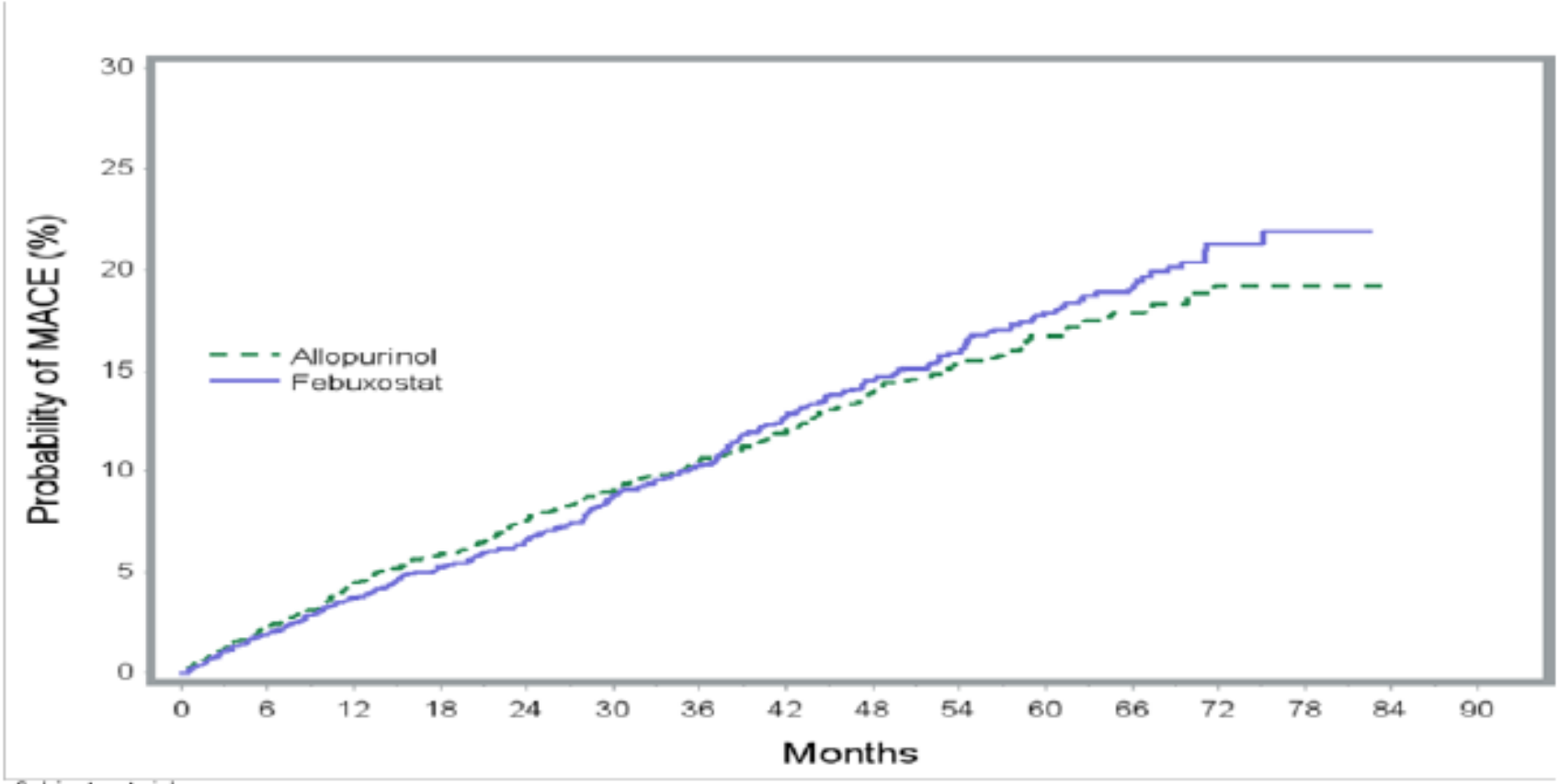
PY=person-year until first MACE or trial discontinuation

[] indicates incidence rate per 100 person-years

Source: Created by the statistical reviewer

CARES Trial Results

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



Subjects at risk

Febuxostat	3098	2776	2478	2081	1817	1552	1339	1120	919	739	541	404	207	48	0
Allopurinol	3092	2761	2444	2048	1766	1516	1324	1093	887	725	554	390	211	48	0

CARES Trial Results

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)

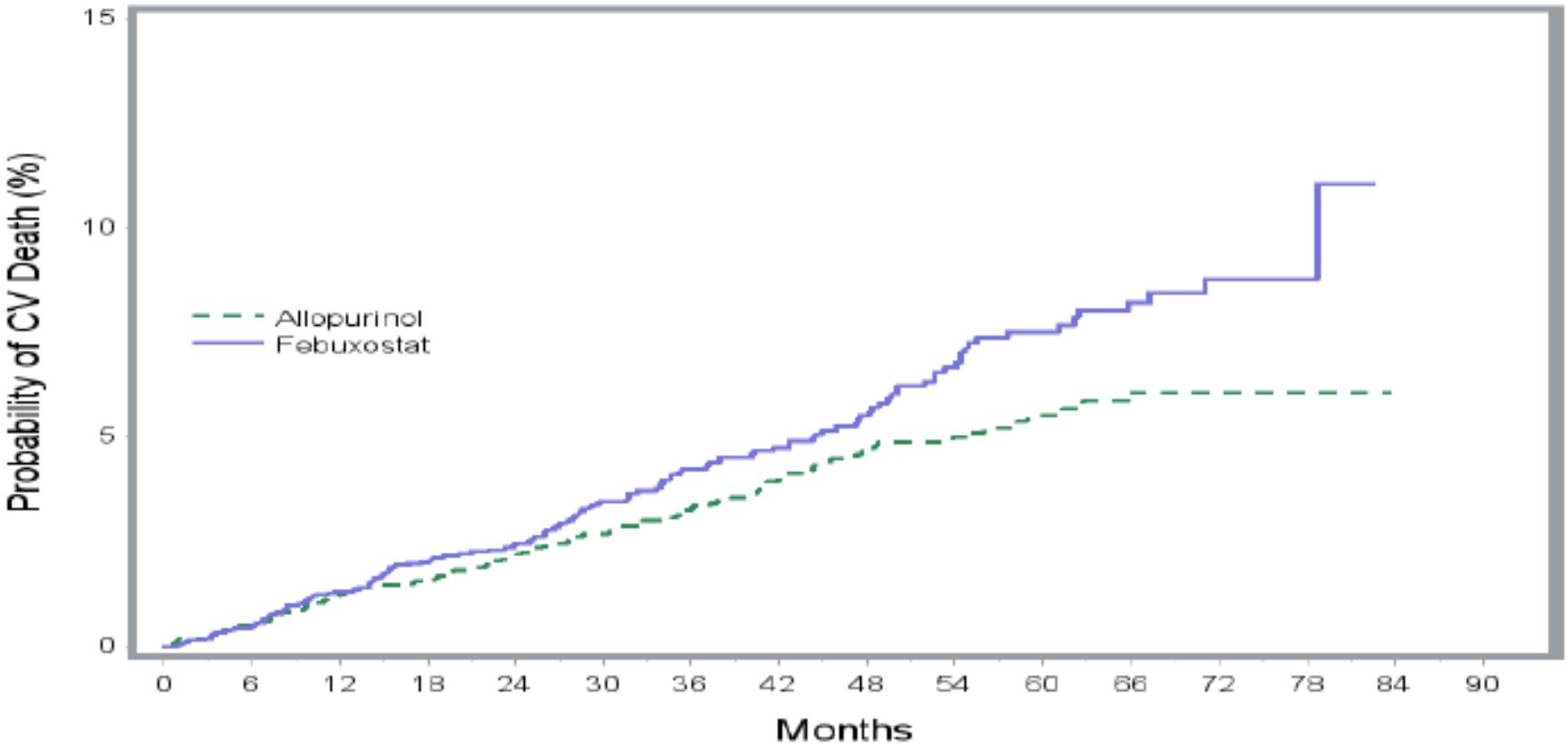
*Hazard Ratio for Febuxostat vs. Allopurinol

[] indicates incidence rate per 100 person-years

Source: Created by the statistical reviewer

CARES Trial Results

Figure 6. Kaplan-Meier Plot for Cardiovascular Death

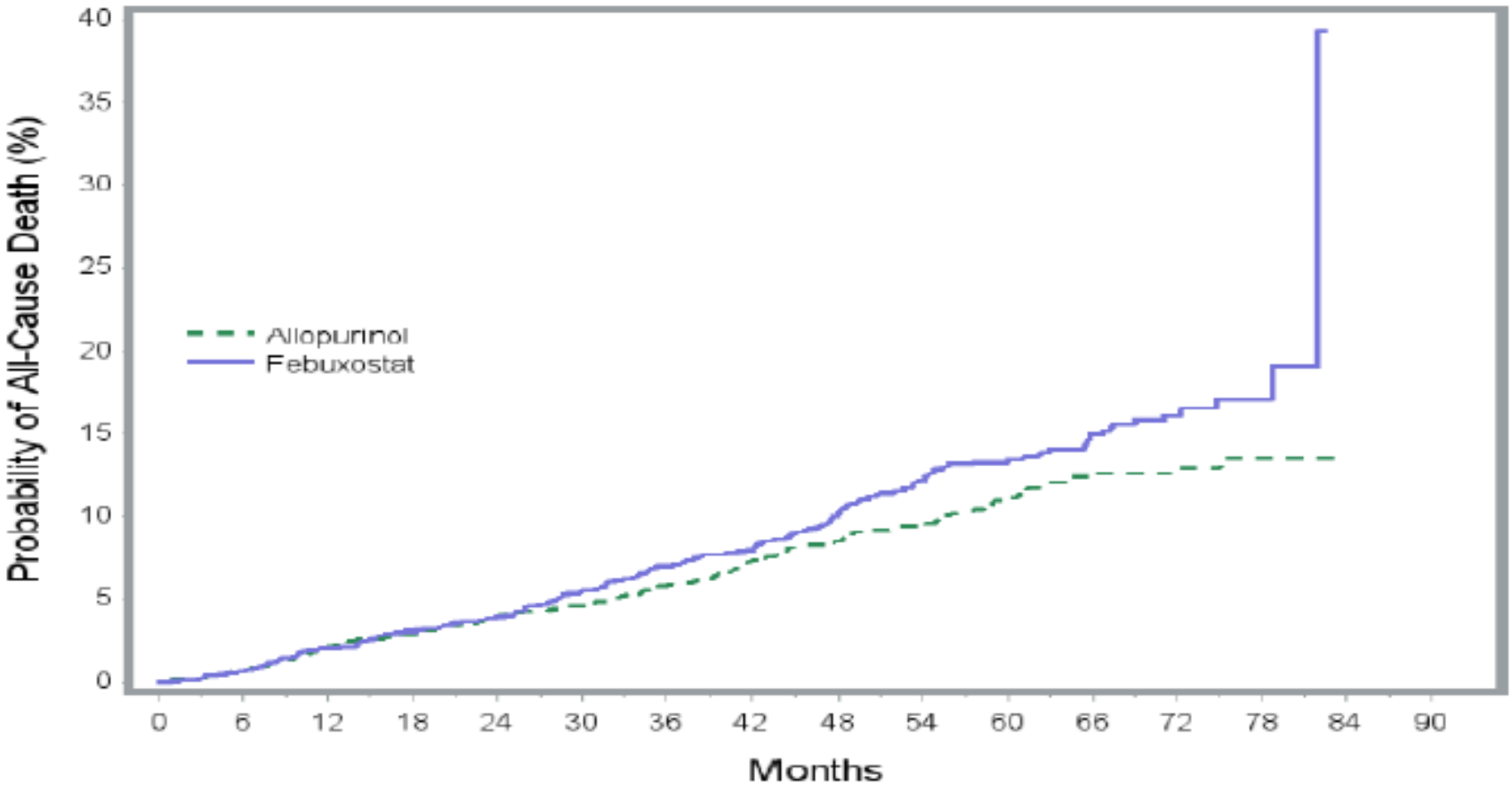


Subjects at risk

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

CARES Trial Results

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

CARES Trial Results

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

CARES Trial Results

- The most common cause of CV 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 CV 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.

CARES Trial Results

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

CARES Trial Results

FDA Briefing Document , Table 29, Excerpts

	Febuxostat N=3092 % (n/N)	
	40 mg	80 mg
MACE	9.6% (180/1884)	12.7% (154/1208)
CV Death	3.6% (68/1884)	5.4% (65/1208)
All-Cause Death	6.5% (122/1884)	9.9% (120/1208)

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

- 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 CARES trial 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.
- 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.

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

- **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% (see Table 6, page 152 of the FDA briefing document).**

Conclusions

- 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.

Conclusions

- 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.