



1600 20th Street, NW • Washington, D.C. 20009 • 202/588-1000 • www.citizen.org

Citizen Petition

Date: June 21, 2018 **[EMBARGOED UNTIL 12:01 AM EDT ON THURSDAY, JUNE 21, 2018]**

On behalf of Public Citizen, a consumer advocacy organization with more than 400,000 members and supporters nationwide, and Public Citizen's Health Research Group, the undersigned submit this petition under Section 355(e) of the Federal Food, Drug, and Cosmetic Act and under Food and Drug Administration (FDA) regulations at 21 C.F.R. § 10.30 to request the Commissioner of Food and Drugs to immediately require the removal from the market of all medications containing the widely prescribed xanthine oxidase inhibitor febuxostat because (1) febuxostat use 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. In summary, febuxostat has unique serious risks but no unique clinical benefit.

A. ACTION REQUESTED

Immediately require removal from the market of all medications containing febuxostat, which is currently marketed under the brand name Uloric.

B. STATEMENT OF GROUNDS

1. Background

Febuxostat is a medication used for the chronic management of hyperuricemia in patients with gout. Gout is a metabolic disease characterized by painful uric acid crystal deposition in the joints, the kidneys, and other tissues that may lead to locally destructive tophi as well as uric acid nephrolithiasis and interstitial kidney disease. Gout typically manifests as chronic monoarthritis or polyarthritis punctuated by episodic painful flares commonly affecting the metatarsophalangeal joint of the first toe, as well as the tarsal joints, ankles, and knees.¹

The mainstays of therapy for acute gout flares include anti-inflammatory drugs such as colchicine, nonsteroidal anti-inflammatory drugs (NSAIDs), and glucocorticoids. The mainstays of therapy for chronic gout include dietary modification to limit the intake of purines, alcohol, and fructose-containing foods; avoidance of exacerbating diuretic medications; increased fluid

¹ Schumacher H, Chen LX. Gout and other crystal-associated arthropathies. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J. eds. *Harrison's Principles of Internal Medicine*. 19th ed. New York, NY: McGraw-Hill; 2014.

intake; and pharmacologic therapy with serum uric acid (SUA)-lowering medications such as xanthine oxidase inhibitors, uricosuric agents, and pegloticase.²

Xanthine oxidase inhibitors such as febuxostat act by blocking the conversion of hypoxanthine to xanthine and xanthine to uric acid, thereby decreasing serum uric acid levels.^{3,4} Initiation of anti-hyperuricemic drug therapy may be associated with a paradoxical short-term increased risk of gout flares, which prophylactic treatment with colchicine or an NSAID can attenuate.⁵ Allopurinol is a purine-analogue xanthine oxidase inhibitor that was approved by the FDA in 1966 for the treatment of gout.⁶ Febuxostat is a non-purine xanthine oxidase inhibitor that was licensed by Takeda Pharmaceuticals North America and approved by the FDA in 2009 for the chronic management of hyperuricemia in patients with gout.⁷

According to data from IMS Health, for the 12-month period that ended June 30, 2015, febuxostat was the 46th most-prescribed branded drug in the U.S., with 1.3 million prescriptions.⁸ Takeda Pharmaceutical Company reported \$1.9 billion in U.S. sales of febuxostat in the six years from fiscal years 2012 through 2017.^{9,10}

2. Initial clinical trials linking febuxostat to possible increased risk of adverse cardiovascular events and death

The Febuxostat Versus Allopurinol Controlled Trial (FACT, C02-010, NCT00102440)¹¹

In 2005, Becker et al. published results of the first phase 3 randomized, controlled trial comparing febuxostat with allopurinol, in which four deaths occurred among 507 subjects receiving febuxostat and no deaths occurred among 253 subjects receiving allopurinol.¹²

² *Ibid.*

³ Prometheus Laboratories Inc. Label: allopurinol (ZYLOPRIM). May 2017. <https://dailymed.nlm.nih.gov/dailymed/getFile.cfm?setid=6fcb546c-d925-47e9-b574-9941dcf360c6&type=pdf&name=6fcb546c-d925-47e9-b574-9941dcf360c6>. Accessed June 11, 2018.

⁴ Takeda Pharmaceuticals America, Inc. Label: febuxostat (ULORIC). February 2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021856s012bl.pdf. Accessed June 11, 2018.

⁵ Burns C, Wortmann RL. Chapter 44. Gout. In: Imboden JB, Hellmann DB, Stone JH, eds. *CURRENT Diagnosis & Treatment: Rheumatology*. 3rd ed. New York, NY: McGraw-Hill; 2013.

⁶ Prometheus Laboratories Inc. Label: allopurinol (ZYLOPRIM). May 2017. <https://dailymed.nlm.nih.gov/dailymed/getFile.cfm?setid=6fcb546c-d925-47e9-b574-9941dcf360c6&type=pdf&name=6fcb546c-d925-47e9-b574-9941dcf360c6>. Accessed June 11, 2018.

⁷ Food and Drug Administration. Approval letter for NDA 21-856. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_Approv.pdf. Accessed June 11, 2018.

⁸ Brooks M. 100 best-selling, most prescribed branded drugs through June. *Medscape*. August 13, 2015. <https://www.medscape.com/viewarticle/849457>. Accessed June 16, 2018.

⁹ Takeda Pharmaceutical Company. Financial Results for FY2014 Data Book. https://www.takeda.com/siteassets/system/investors/report/quarterlyannouncements/fy2014/fy2014-full-year-results-released-on-may-15-2015/qr2014_full_d_en.pdf. Accessed June 16, 2018. PDF p. 9.

¹⁰ Takeda Pharmaceutical Company. FY2017 Data Book. https://www.takeda.com/siteassets/system/investors/report/quarterlyannouncements/fy2017/fy2017-full-year-results/qr2017_q4_d01_en.pdf. Accessed June 16, 2018. PDF p. 26.

¹¹ U.S. National Library of Medicine. ClinicalTrials.gov. Febuxostat versus allopurinol control trial in subjects with gout (FACT; NCT00102440). 2012. <https://clinicaltrials.gov/ct2/show/NCT00102440>. Accessed June 11, 2018.

¹² 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.

FACT was a double-blind, randomized, multicenter trial comparing febuxostat at doses of 80 milligrams (mg) or 120 mg with allopurinol at a dose of 300 mg once daily for 52 weeks. The FACT investigators enrolled patients with gout and hyperuricemia ($\text{SUA} \geq 8$ mg/deciliter [dL]) and excluded those with abnormal renal function (serum creatinine [SCr] > 1.5 mg/dL or estimated glomerular filtration rate < 50 milliliters [mL]/minute [min]/1.73 square meters body surface area [m^2]). Colchicine or naproxen for gout flare prophylaxis was administered to all subjects for the first eight weeks of the trial. The primary endpoint for the trial was an SUA concentration below 6 mg/dL at each of the last three monthly measurements. Of the 760 subjects, 96% were male and 77% were white.

The trial found that a higher percentage of subjects taking febuxostat at both the 80-mg and 120-mg doses achieved the primary endpoint than those taking allopurinol (53% and 62% vs. 21%, respectively; $p < 0.001$ for both comparisons). The trial also found a higher incidence of self-reported gout flares during the first eight weeks of the drug intervention among subjects receiving the 120-mg dose of febuxostat compared with those receiving the 80-mg dose and those receiving allopurinol (36% vs. 22% and 21%, respectively; $p < 0.001$ for both comparisons). There were no statistically significant differences among the trial groups in the percentage reduction in tophus area or in the reduction in the number of tophi.

FACT demonstrated a numerically higher rate of death among febuxostat-exposed subjects, with four subjects (0.8%) receiving febuxostat dying and no subjects receiving allopurinol dying during the trial. Two of the deaths occurred in subjects receiving 80 mg of febuxostat daily, with one death attributed to respiratory failure secondary to septic shock, congestive heart failure, and coronary artery disease in a 65-year-old man hospitalized for severe joint pain and the other to a retroperitoneal hemorrhage in a 77-year-old man with atrial fibrillation and heart failure on anticoagulation therapy. The other two deaths occurred in subjects receiving 120 mg of febuxostat daily, with one death attributed to anoxic encephalopathy secondary to cardiac and respiratory arrest after carotid endarterectomy in a 68-year-old man and the other to metastatic colon cancer in a 74-year-old man.¹³ The trial authors stated that “all deaths were judged by the investigators to be unrelated to study drugs” and noted that the difference in the number of deaths between the trial groups was not statistically significant ($p = 0.31$).¹⁴

*The Allopurinol- and Placebo-Controlled Efficacy Study of Febuxostat (APEX, C02-009, NCT00174915)*¹⁵

In 2008, Schumacher et al. published the results of APEX, the second phase 3 randomized, controlled trial comparing febuxostat with allopurinol; unlike FACT, APEX also included a

¹³ Food and Drug Administration. Medical review for NDA 21-856. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_MedR_P3.pdf. Accessed June 11, 2018. PDF pp. 4-7.

¹⁴ 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.

¹⁵ U.S. National Library of Medicine. ClinicalTrials.gov. Phase 3, febuxostat, allopurinol, and placebo-controlled study in gout subjects (APEX; NCT00174915). 2012. <https://clinicaltrials.gov/ct2/show/NCT00174915>. Accessed June 11, 2018.

placebo group.¹⁶ This trial showed higher rates of serious adverse events among febuxostat-exposed subjects than among allopurinol- or placebo-exposed subjects (3.7% vs. 2.6% vs. 1.5%, respectively), although the differences were not statistically significant, and no deaths were reported.

APEX was a double-blind, randomized, multicenter 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. The number of subjects enrolled in each trial group was as follows: febuxostat 80 mg, 267; febuxostat 120 mg, 269; febuxostat 240 mg, 134; allopurinol, 268; and placebo, 134. The APEX investigators enrolled 1,072 subjects with gout and hyperuricemia ($\text{SUA} \geq 8 \text{ mg/dL}$) and included those with normal renal function ($\text{SCr} \leq 1.5 \text{ mg/dL}$) as well as a small number ($n=40$) with mild-to-moderate renal dysfunction ($\text{SCr} > 1.5$ to $\leq 2 \text{ mg/dL}$). All subjects received colchicine or naproxen for gout flare prophylaxis during the first eight weeks of the study. The primary endpoint was the same as in the earlier FACT trial: an SUA level below 6 mg/dL at each of the last three monthly measurements. Ninety-four percent of the subjects were male and 78% were white.

The trial found that higher percentages of subjects receiving febuxostat 80 mg (48%), 120 mg (65%), and 240 mg (69%) achieved the primary endpoint than those receiving allopurinol (22%, $p < 0.001$ for all three comparisons) or placebo (0%, $p < 0.001$ for all three comparisons). During the first eight weeks of trial drug intervention, more subjects receiving febuxostat 120 mg (36%) and 240 mg (46%) required treatment for gout flares than did those receiving febuxostat 80 mg (28%), allopurinol (23%), and placebo (20%) ($p \leq 0.05$ for all comparisons). There were no statistically significant differences between trial groups in the proportions of subjects receiving treatment for gout flares after eight weeks of trial drug intervention. No significant differences in the number of tophi were observed between trial groups, with the exception of a mean percent decrease in the number of tophi observed with febuxostat 120 mg (-1.2) versus placebo (-0.3) at week 28 ($p \leq 0.05$). There were also no significant differences in reductions in median tophus size from baseline between trial groups.

Regarding safety outcomes, Schumacher et al. reported a numerically greater proportion of subjects experiencing serious adverse events in the febuxostat 80 mg (11 of 267, 4.1%), 120 mg (9 of 269, 3.3%), and 240 mg (5 of 134, 3.7%) groups than in the allopurinol (7 of 268, 2.6%) and placebo (2 of 134, 1.5%) groups. However, these differences were not statistically significant. Serious adverse cardiovascular events (chest pain, coronary artery disease, myocardial infarction, and atrial fibrillation) occurred more frequently in the febuxostat 80 mg (5 of 267, 1.9%), 120 mg (5 of 269, 1.9%), and 240 mg (1 of 134, 0.7%) and placebo (1 of 134, 0.7%) groups than in the allopurinol (1 of 268, 0.4%) group. These differences were not statistically significant.

¹⁶ Schumacher HR, Becker MA, Wortmann RL, et al. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: A 28-week, phase III, randomized, double-blind, parallel-group trial. *Arthritis Care Res.* 2008;59(11):1540-1548.

Long-term open-label extension trials

Two long-term open-label extension trials — the Febuxostat Open-Label Clinical Trial of Urate-Lowering Efficacy and Safety (FOCUS, TMX-01-005, NCT00174941)¹⁷ and the Febuxostat/Allopurinol Comparative Extension Long-Term Study (EXCEL, CO2-021, NCT00175019)¹⁸— enrolled subjects from the randomized, double-blind phase 2 and phase 3 trials, respectively, to examine long-term safety and efficacy of febuxostat.

The FOCUS trial was a 5-year continuation of a 28-day phase 2 dose-response trial (TMX-00-004, NCT00174967) in which 153 subjects were randomly assigned to febuxostat (at a dose of 40 mg, 80 mg, or 120 mg) or placebo once daily.^{19,20} For FOCUS, 116 subjects who had completed the phase 2 trial initially received febuxostat at a dosage of 80 mg once daily and subsequently had the febuxostat dosage titrated between weeks 4 and 24 from 40 to 120 mg once daily to achieve a target SUA of less than 6 mg/dL and at least 3 mg/dL.²¹ After 24 weeks, subjects were maintained on a stable febuxostat dose.

The EXCEL trial enrolled 1,086 subjects who had completed either the FACT or APEX phase 3 trials. For the EXCEL trial, subjects initially were assigned to receive febuxostat 80 mg or 120 mg (650 and 291 subjects, respectively) or allopurinol (145 subjects) daily. Note that the first 351 subjects received febuxostat 80 mg once daily, with titration up to 120 mg over six months to achieve a target SUA of less than 6 mg/dL and at least 3 mg/dL. After an amendment requested by the FDA, the remaining subjects were randomly assigned to one of the three trial groups and were permitted to switch between treatment groups to achieve a target SUA of less than 6 mg/dL and at least 3 mg/dL through the first six months of the trial. The EXCEL subjects were monitored for 40 months after enrollment.²²

The FOCUS and EXCEL long-term extension trials were ongoing when the new drug application (NDA) for febuxostat was first submitted to the FDA.

¹⁷ U.S. National Library of Medicine. ClinicalTrials.gov. Long-term safety of febuxostat in subjects with gout (NCT00174941). 2011. <https://clinicaltrials.gov/ct2/show/NCT00174941>. Accessed June 11, 2018.

¹⁸ U.S. National Library of Medicine. ClinicalTrials.gov. Allopurinol versus febuxostat in subjects completing the phase 3 trials C02-009 or C02-010 (NCT00175019). 2010. <https://clinicaltrials.gov/ct2/show/NCT00175019>. Accessed June 11, 2018.

¹⁹ U.S. National Library of Medicine. ClinicalTrials.gov. Dose-response, safety and efficacy of febuxostat in subjects with gout (NCT00174967). 2011. <https://clinicaltrials.gov/ct2/show/NCT00174967>. Accessed June 11, 2018.

²⁰ Becker MA, Schumacher HR, Wortmann RL, et al. Febuxostat, a novel nonpurine selective inhibitor of xanthine oxidase: A twenty-eight-day, multicenter, phase II, randomized, double-blind, placebo-controlled, dose-response clinical trial examining safety and efficacy in patients with gout. *Arthritis Rheum.* 2005;52(3):916-923.

²¹ Schumacher HR, Becker MA, Lloyd E, et al. Febuxostat in the treatment of gout: 5-yr findings of the FOCUS efficacy and safety study. *Rheumatology.* 2009;48(2):188-194.

²² Becker MA, Schumacher HR, MacDonald PA, et al. Clinical efficacy and safety of successful longterm urate lowering with febuxostat or allopurinol in subjects with gout. *J Rheumatol.* 2009;36(6):1273-1282.

3. FDA assessments and actions

First New Drug Application (NDA) Submission

TAP Pharmaceutical Products submitted its initial NDA (NDA 21-856) in December 2004 seeking approval for 80-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.”²³

The initial NDA presented efficacy and safety data from 24 phase 1 trials; the 28-day dose-response phase 2 trial (TMX-00-004) and its long-term extension trial (FOCUS, TMX-01-005); and the phase 3 FACT and APEX trials and their long-term extension trial (EXCEL, CO2-021) for the U.S. clinical development program.²⁴

In their assessment of the initial submission, the FDA reviewers noted that eight deaths had occurred in the phase 2 and 3 trials among subjects who received febuxostat, including two deaths due to myocardial infarction, whereas no subject deaths occurred in the allopurinol and placebo comparator groups.²⁵ Most of the deaths occurred after 170 days of febuxostat exposure.²⁶ The FDA noted that review of the subjects’ narratives in most cases did not allow the exclusion of a possible causal association with febuxostat, with the possible exception of one death due to metastatic colon cancer.²⁷ At the time of the first NDA submission, four of the eight reported deaths had occurred in the then-ongoing EXCEL long-term extension trial.²⁸

FDA reviewers also expressed significant concern about an excess of serious adverse cardiovascular events in febuxostat-group subjects. For example, 17 ischemic coronary artery disease adverse events (acute coronary syndrome, acute myocardial infarctions, angina, and myocardial infarction) occurred in 1,707 febuxostat-exposed subjects, whereas two such events occurred in 692 allopurinol-exposed subjects and none occurred in 172 placebo-group subjects.²⁹ FDA reviewers also noted an excess of cerebrovascular events (stroke and transient ischemic

²³ 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 June 11, 2018. PDF p. 53.

²⁴ Food and Drug Administration. Medical review for NDA 21-856. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_MedR_P2.pdf. Accessed June 11, 2018. PDF p. 92.

²⁵ Food and Drug Administration. Medical review for NDA 21-856. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_MedR_P3.pdf. Accessed June 11, 2018. PDF p. 1.

²⁶ *Ibid.* PDF p. 8.

²⁷ Food and Drug Administration. Medical review for NDA 21-856. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_MedR_P4.pdf. Accessed June 11, 2018. PDF p. 11.

²⁸ Food and Drug Administration. Medical review for NDA 21-856. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_MedR_P3.pdf. Accessed June 11, 2018. PDF pp. 1-2.

²⁹ *Ibid.* PDF p. 26.

attack) (9 events) and cardiac arrest events (2 events) among the 1,707 febuxostat-exposed subjects, whereas no such events occurred in the 692 allopurinol-exposed subjects or the 172 placebo-group subjects.

In terms of efficacy, FDA reviewers concluded that there was substantial evidence of efficacy to support the sponsor's proposed indication for febuxostat (management of hyperuricemia associated with gout).³⁰ 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.³¹

The lead FDA clinical reviewer concluded that "the risk/benefit analysis is not favorable for [febuxostat] at this time."³² He also recommended that "[t]he sponsor should be requested to provide additional efficacy and safety data preferably from an additional trial or trials as follows: the sponsor should address the issue of cardiovascular safety; it is likely that a large outcome study will be required." The FDA appropriately decided not to approve the NDA for febuxostat and on October 14, 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."³³ The FDA required that the sponsor submit additional safety data for febuxostat from "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." The approvable letter also requested further efficacy data showing that febuxostat "impacts some important outcome for gout patients, beyond the surrogate of uric acid levels, since the design and results of the submitted studies do not allow for [the FDA] to conclude that the efficacy of [febuxostat] in lowering serum uric acid levels leads to a reduction in gouty flairs [*sic*], tophus size or other important manifestations of gout with chronic use."³⁴

Second NDA submission

In February 2006, TAP Pharmaceutical Products submitted the first supplement (S-01) to NDA 21-856 to the FDA for approval of 80-mg and 120-mg once-daily febuxostat tablets, again for management of hyperuricemia in patients with gout.³⁵ The supplemental NDA included a

³⁰ Food and Drug Administration. Medical review for NDA 21-856. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_MedR_P4.pdf. Accessed June 11, 2018. PDF p. 54.

³¹ *Ibid.* PDF p. 86.

³² *Ibid.* PDF p. 54.

³³ Food and Drug Administration. Approvable letter(s) for NDA 21-856. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_Approvable.pdf. Accessed June 11, 2018. PDF p. 6.

³⁴ *Ibid.* PDF p. 7.

³⁵ Food and Drug Administration. Medical review for NDA 21-856. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_MedR_P1.pdf. Accessed June 11, 2018. PDF p. 84.

reanalysis of the prior clinical trial data augmented by new data from the two then-ongoing long-term extension clinical trials (FOCUS, TMX-01-005; and EXCEL, CO2-021).³⁶ The reanalysis included post-hoc adjudication of adverse events by a single, sponsor-hired cardiologist and categorization of adverse events according to Antiplatelet Trialists Collaboration (APTC) primary and secondary events.³⁷ The APTC system was developed in the 1990s for meta-analysis of randomized clinical trials that assessed the benefits of antiplatelet therapy and has subsequently been used in meta-analyses assessing cardiovascular adverse events in clinical trials testing analgesic and other medications.^{38,39,40} The primary APTC events used in the reanalysis included cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and non-fatal cardiac arrest.⁴¹ The secondary APTC events included angina, revascularization, transient ischemic attack, venous and peripheral arterial vascular thrombotic events, and non-fatal congestive heart failure.

The sponsor's expert reviewer, cardiologist Dr. William White, performed adjudication of all available clinical information related to serious cardiovascular events (n=113) while blinded to treatment arm assignment in the phase III and long-term extension studies.⁴² The adjudication by the sponsor's expert reviewer resulted in a lower total number of APTC events reported in Phase 3 trials.⁴³ The FDA's Division of Anesthesia, Analgesia and Rheumatology Products consulted the agency's Division of Cardiovascular and Renal Products (DCRP) for an assessment of the expert adjudication, and the DCRP consultant found the adjudication "not helpful due to a paucity of detail in the [case report forms] regarding the events and to an absence of appropriate criteria that would allow a fair and reasoned readjudication."⁴⁴ The DCRP reviewer nonetheless also attempted their own readjudication of a subset of the adverse events but concluded that such efforts were "largely an exercise in futility" due to the lack of pre-specified "criteria for most events" and the lack of "clinical information for most criteria."⁴⁵ In general, FDA reviewers believed that the original investigator-reported events were adequate to identify and categorize the adverse cardiovascular events and that "precise adjudication is not needed."⁴⁶

³⁶ *Ibid.* PDF pp. 89-90.

³⁷ *Ibid.* PDF p. 90.

³⁸ Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy – I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ*. 1994;308:81-106.

³⁹ White WB, Faich G, Borer JS, Makuch RW. Cardiovascular thrombotic events in arthritis trials of the cyclooxygenase-2 inhibitor celecoxib. *Am J Cardiol*. 2003;92(4):411-418.

⁴⁰ Zarbin MA, Dunger-Baldauf C, Haskova Z, et al. Vascular safety of ranibizumab in patients with diabetic macular edema: A pooled analysis of patient-level data from randomized clinical trials. *JAMA Ophthalmol*. 2017;135(5):424-431.

⁴¹ Food and Drug Administration. Medical review for NDA 21-856.

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_MedR_P2.pdf. Accessed June 11, 2018. PDF p. 56.

⁴² *Ibid.* PDF pp. 4 & 6.

⁴³ *Ibid.* PDF pp. 58-62.

⁴⁴ Food and Drug Administration. Medical review for NDA 21-856.

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_MedR_P1.pdf. Accessed June 11, 2018. PDF p. 80.

⁴⁵ Food and Drug Administration. Medical review for NDA 21-856.

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_MedR_P2.pdf. Accessed June 11, 2018. PDF p. 74.

⁴⁶ *Ibid.* PDF p. 49.

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.⁴⁷ Although the febuxostat groups had more total person-years of exposure than the allopurinol control groups in the randomized controlled trials (671 person-years exposed to febuxostat vs. 334 person-years exposed to allopurinol) and long-term extension studies (2,121 person-years exposed to febuxostat vs. 145 person-years exposed to allopurinol), this difference in exposure did not fully account for the difference in deaths.⁴⁸ The combined all-cause mortality rate for febuxostat-exposed subjects in the phase 3 randomized controlled trials and in the long-term extension trials was 0.43 deaths per 100 person-years compared with 0 deaths per 100 person-years among allopurinol-exposed subjects based on updated data as of February 8, 2006. The all-cause mortality rate for febuxostat-exposed subjects in the randomized controlled trials was 0.60 deaths per 100 person-years, whereas the mortality rate of febuxostat-exposed subjects in the long-term extension studies was 0.38 deaths per 100 person-years,⁴⁹ a difference possibly attributable, in part, to depletion of a vulnerable subpopulation prior to enrollment in open-label extension trials due to either death or nonfatal adverse events.

Nine of the 12 deaths among febuxostat-exposed subjects were attributable to cardiovascular causes, including five related to myocardial infarction.⁵⁰ The cardiovascular mortality rate for febuxostat-exposed subjects in randomized controlled trials was 0.45 deaths per 100 person-years and in all trials, including the long-term extension trials, was 0.36 deaths per 100 person-years compared with 0 deaths per 100 person-years in the allopurinol-exposed subjects.

Focusing on composite cardiovascular events categorized by APTC criteria, FDA reviewers again noted a numerical excess of investigator-reported primary and secondary APTC events. In the phase 3 randomized controlled 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).⁵¹ Analyzing investigator-reported treatment-emergent primary and secondary APTC events together, cardiovascular complications were more common in febuxostat-exposed subjects (25 of 1,177, or 2.1%) than in allopurinol-exposed subjects (7 of 521, or 1.3%) or placebo-group subjects (1 of 134, or 0.7%) in the phase 3 randomized controlled trials.⁵² The most common APTC events in the phase 3 clinical trials in febuxostat-exposed subjects were angina, revascularization, and non-fatal myocardial infarction, and all

⁴⁷ Food and Drug Administration. Medical review for NDA 21-856.

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_MedR_P1.pdf. Accessed June 11, 2018. PDF p. 91.

⁴⁸ *Ibid.* PDF p. 94.

⁴⁹ *Ibid.* PDF p. 94.

⁵⁰ *Ibid.* PDF pp. 95-96.

⁵¹ Food and Drug Administration. Medical Review for NDA 21-856.

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_MedR_P2.pdf. Accessed June 11, 2018. PDF p. 9.

⁵² *Ibid.* PDF p. 11.

categories of APTC events except revascularization were more common among febuxostat-exposed subjects than allopurinol-exposed subjects.

In the long-term extension trials, the investigator-reported treatment-emergent primary APTC event rate among febuxostat-exposed subjects was 1.50 events per 100 person-years (29 events in 1,934 person-years). The rate in allopurinol-exposed subjects was 0.75 events per 100 person-years (1 event in 133 person-years).⁵³

The FDA concluded that the cardiovascular safety data for febuxostat remained a significant concern and required further study prior to reconsideration of whether to approve the drug. For example, one of the primary clinical reviewers opposed approval, offering the following overall assessment:

This reviewer recommends non-approvable action for febuxostat 80 mg and 120 mg tablets for the treatment of hyperuricemia in patients with gout based on an unfavorable risk/benefit profile. Initial review cycle raised concerns regarding the potential for febuxostat 80-mg and 120-mg doses to cause cardiovascular (CV)/thrombotic adverse events (AE) in excess of that seen with allopurinol or placebo. Reanalyses of existing data and additional analyses of new data did not eliminate safety concerns raised in initial review. Of further concern, the efficacy of febuxostat 80 mg and 120 mg was established based on a surrogate endpoint without sufficient evidence of clinical efficacy.⁵⁴

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

This complete response does not adequately address the cardiovascular safety concerns noted during the first review cycle for the application. While I think that some of Dr. Oussova's analyses may have overestimated the actual relative risk of cardiovascular thromboembolic events, I am convinced by the review team's assessment that a clear signal of risk remains, even in the most cautious analysis. ... the 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.⁵⁵

Due to the aforementioned deficiencies, the FDA again appropriately denied approval of febuxostat and issued a second approvable letter on August 2, 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

⁵³ *Ibid.* PDF p. 12.

⁵⁴ Food and Drug Administration. Medical review for NDA 21-856. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_MedR_P1.pdf. Accessed June 11, 2018. PDF p. 86.

⁵⁵ *Ibid.* PDF p. 81.

risk-benefit characteristics has been defined.”⁵⁶ In discussing the design of a new study to provide this additional data, the agency stated that “it would be important that the study be designed in such a manner as to collect an adequate number of cardiovascular adverse events to reach conclusions about the cardiovascular safety of febuxostat.”⁵⁷ In addition, the approvable letter described a pre-existing commitment of the sponsor to conduct “A Randomized, Multicenter Study Comparing the Efficacy and Safety of Febuxostat to Allopurinol in Reducing the Incidence of Gout Flares in Subjects with Gout.”⁵⁸

Third NDA submission

In response to the FDA’s ongoing concerns regarding the cardiovascular safety of febuxostat, Takeda Pharmaceuticals North America (the parent company of TAP Pharmaceutical Products) undertook the Confirmation of Febuxostat in Reducing and Maintaining Serum Urate trial (CONFIRMS trial, F-GT06-153, NCT00430248),⁵⁹ a double-blind, randomized multicenter trial that compared febuxostat (40 mg or 80 mg) with allopurinol dosed daily over six months in subjects with gout and hyperuricemia (SUA \geq 8 mg/dL).⁶⁰ The trial excluded patients with severe renal impairment (estimated creatinine clearance [eCLcr]<30 mL/min). Those assigned to the control group received 300 mg of allopurinol daily if they had normal or mildly impaired renal function (eCLcr \geq 60 mL/min) or 200 mg of allopurinol daily if they had moderately impaired renal function (eCLcr<60 mL/min and \geq 30 mL/min). Colchicine or naproxen for gout flare prophylaxis was administered to all subjects for the duration of the study. 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, which was different from prior FACT and APEX phase 3 trials, for which the primary endpoint was an SUA concentration below 6 mg/dL at each of the last three monthly measurements. The CONFIRM trial enrolled 2,269 subjects (757 in the febuxostat 40-mg group, 756 in the febuxostat 80-mg group, and 756 in the allopurinol group) and was sized to achieve 90% power to meet the non-inferiority criteria between febuxostat 40 mg and allopurinol and the ability to detect a 10% difference between any two groups for the primary efficacy endpoint. All deaths and adverse events considered by the investigators to be potentially cardiovascular-related were blindly adjudicated by a cardiovascular endpoints committee

⁵⁶ Food and Drug Administration. Approvable letter(s) for NDA 21-856.

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_Approvable.pdf. Accessed June 11, 2018. PDF p. 2.

⁵⁷ Food and Drug Administration. Medical review for NDA 21-856.

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_MedR_P1.pdf. Accessed June 11, 2018. PDF p. 27.

⁵⁸ Food and Drug Administration. Approvable letter(s) for NDA 21-856.

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_Approvable.pdf. Accessed June 11, 2018. PDF p. 3.

⁵⁹ U.S. National Library of Medicine. ClinicalTrials.gov. Efficacy and safety of oral febuxostat in participants with gout (NCT00430248). 2012. <https://clinicaltrials.gov/ct2/show/NCT00430248>. Accessed June 11, 2018.

⁶⁰ 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.

composed of two cardiologists and one neurologist.⁶¹ Study subjects were 94% male and 82% white.⁶²

Results of the CONFIRMS trial were published by Becker et al. in 2009 and 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).⁶³ 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. The trial investigators also did not assess for reduction in tophus area or tophi number.

In terms of safety, there were two deaths among the febuxostat-exposed subjects and three deaths among the allopurinol-exposed subjects. One subject who received febuxostat 40 mg died in his sleep after being bitten by fire ants at work. This death was adjudicated as non-cardiovascular; however, FDA reviewers later judged this death to be an unexplained sudden death and therefore a cardiovascular death.⁶⁴ Another subject who received febuxostat 80 mg died from brain edema and chronic obstructive pulmonary disease. The three deaths among allopurinol-treated subjects were attributed to necrotizing pneumonia and sepsis after lung carcinoma resection, hypertensive heart disease, and sudden death; the latter two were attributed to cardiovascular causes.⁶⁵

Three subjects in the febuxostat 80-mg group and three subjects in the allopurinol group experienced primary APTC events, whereas none in the febuxostat 40-mg group experienced such events. The CONFIRMS trial investigators reported a similar proportion of subjects experiencing secondary APTC events in the febuxostat 40-mg (7 of 757, 0.92%), febuxostat 80-mg (3 of 756, 0.40%), and allopurinol (6 of 756, 0.79%) groups.⁶⁶ The proportion of subjects experiencing non-APTC cardiovascular event rates was similar in the febuxostat 40-mg (10 of 757, 1.32%), febuxostat 80-mg (9 of 756, 1.19%), and allopurinol (7 of 756, 0.93%) groups.⁶⁷

After the completion of the CONFIRMS trial, Takeda Pharmaceuticals North America submitted a revised NDA to the FDA for approval of febuxostat 40-mg and 80-mg tablets dosed daily for the treatment of hyperuricemia associated with gout in July 2008.⁶⁸

⁶¹ Food and Drug Administration. Medical Review for NDA 21-856.

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_MedR_P1.pdf. Accessed May 4, 2018. PDF p. 28.

⁶² 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.

⁶³ *Ibid*.

⁶⁴ Food and Drug Administration. Medical review for NDA 21-856.

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_MedR_P1.pdf. Accessed June 11, 2018. PDF p. 50.

⁶⁵ 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.

⁶⁶ Food and Drug Administration. Medical review for NDA 21-856.

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_MedR_P1.pdf. Accessed June 11, 2018. PDF p. 48.

⁶⁷ *Ibid*. PDF p. 52.

⁶⁸ *Ibid*. PDF p. 19.

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 controlled 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.⁶⁹ 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.”⁷⁰

FDA reviewers’ pooled data from the three phase 3 randomized controlled trials (FACT, APEX, and CONFIRMS) and the two long-term extension studies (FOCUS and EXCEL) demonstrated slightly increased rates of adverse cardiovascular events in febuxostat-exposed subjects compared with allopurinol-exposed subjects but no differences in the rates of all-cause or cardiovascular mortality. For adjudicated APTC events, pooled data across all phase 3 randomized controlled trials showed a relative risk of 1.19 for febuxostat-exposed subjects compared with allopurinol-exposed subjects, with a 95% CI of 0.4 to 3.8.⁷¹ FDA reviewers noted, therefore, “that it is not possible to exclude either a greater or a lower risk with febuxostat with much confidence.”

Pooled data from all phase 3 randomized controlled trials showed no difference in rate of death from any cause between febuxostat-exposed subjects (6 of 2,690, 0.22%) and allopurinol-exposed subjects (3 of 1,277, 0.23%).⁷² Adjusting for duration of exposure in the pooled phase 3 randomized controlled trials, the death rate among all febuxostat-exposed subjects was 0.4 deaths per 100 person-years; the rate was 0.5 deaths per 100 person-years among allopurinol-exposed subjects.⁷³ Pooled data across all phase 3 randomized controlled trials also showed no significant difference in the frequency of cardiovascular death in febuxostat-exposed subjects (3 of 2,690, 0.1%) compared with allopurinol-exposed subjects (2 of 1,277, 0.2%).

FDA reviewers’ analysis of pooled data from the long-term extension trials, which included two additional deaths and 500 person-years of additional follow-up since the second NDA submission, resulted in no significant change in the mortality risk assessment from the prior review: The mortality rate among febuxostat-exposed subjects remained 0.38 deaths per 100

⁶⁹ 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 June 11, 2018. PDF p. 20.

⁷⁰ Food and Drug Administration. Office director memo for NDA 21-856. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_ODMemo.pdf. Accessed June 11, 2018. PDF p. 5.

⁷¹ Food and Drug Administration. Medical review for NDA 21-856. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_MedR_P1.pdf. Accessed June 11, 2018. PDF p. 56.

⁷² *Ibid.* PDF p. 46.

⁷³ Food and Drug Administration. Statistical review for NDA 21-856. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_StatR_P1.pdf. Accessed June 11, 2018. PDF pp. 38-39.

person-years and 0 deaths among allopurinol-exposed subjects.⁷⁴ The rate of investigator-reported primary APTC events in the long-term extension studies was slightly lower among febuxostat-exposed subjects than that seen at the time of the second NDA submission (1.2 vs. 1.4 events per 100 person-years); however, the updated rate for febuxostat-exposed subjects still exceeded the rate for allopurinol-exposed subjects (0.6 events per 100 person-years).⁷⁵ There was no difference in the rates of secondary APTC events between groups in long-term extension studies.

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.^{76,77,78} The FDA's Arthritis Advisory Committee met on November 24, 2008, to discuss the NDA for febuxostat and voted 12 to 0, with 1 abstention, to recommend FDA approval of the drug with a requirement for postmarket studies to further assess the drug's safety.⁷⁹

On February 13, 2009, the FDA issued an approval letter to Takeda Pharmaceuticals North America for the use of febuxostat for the chronic management of hyperuricemia in patients with gout.⁸⁰ FDA reviewers recognized that routine pharmacovigilance would be inadequate to address the major safety concern regarding the potentially increased risk of adverse cardiovascular thromboembolic events with febuxostat, given the expected incidence of adverse cardiovascular events in the population of chronic gout patients.⁸¹ Therefore, as a condition of approval, the FDA required that the sponsor perform a "randomized, controlled trial of adequate size and duration 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."⁸² The FDA stipulated that the trial should start by January 31, 2010, and be completed by January 31, 2014, with a final report to be submitted to the FDA by January 31, 2015.

⁷⁴ Food and Drug Administration. Medical review for NDA 21-856.
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_MedR_P1.pdf. Accessed June 11, 2018. PDF pp. 45-46.

⁷⁵ *Ibid.* PDF p. 48.

⁷⁶ *Ibid.* PDF p. 63.

⁷⁷ 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 June 11, 2018. PDF pp. 21-22.

⁷⁸ Food and Drug Administration. Statistical review for NDA 21-856.
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_StatR_P1.pdf. Accessed June 11, 2018. PDF p. 6.

⁷⁹ Food and Drug Administration. Summary minutes of the Arthritis Advisory Committee. November 24, 2008.
<https://wayback.archive-it.org/7993/20170403222224/https://www.fda.gov/ohrms/dockets/ac/08/minutes/2008-4387m1-final.pdf>. Accessed June 11, 2018. PDF p. 5.

⁸⁰ Food and Drug Administration. Approval letter for NDA 21-856.
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_Approv.pdf. Accessed June 11, 2018.

⁸¹ 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 June 11, 2018. PDF p. 23.

⁸² Food and Drug Administration. Approval letter for NDA 21-856.
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_Approv.pdf. Accessed June 11, 2018. PDF p. 4.

Notably, approval of febuxostat might not have occurred without the ability of the FDA to mandate postmarketing clinical trials under the authority of Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA), a provision that took effect in March 2008.⁸³ 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 approve or not may have been different."⁸⁴ 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."⁸⁵

The initial FDA-approved labeling for febuxostat included the following in the WARNINGS AND PRECAUTIONS section:

In the randomized controlled studies, there was a higher rate of cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) in patients treated with [febuxostat] [0.74 per 100 P-Y (95% CI 0.36-1.37)] than allopurinol [0.60 per 100 P-Y (95% CI 0.16-1.53)] [see Adverse Reactions (6.1)]. A causal relationship with [febuxostat] has not been established. Monitor for signs and symptoms of myocardial infarction (MI) and stroke.⁸⁶

4. Strong confirmatory evidence of harm from febuxostat

On November 15, 2017, the FDA issued a drug safety communication alerting the public that preliminary results from the FDA-mandated post-market randomized controlled trial to assess the safety of febuxostat showed an increased risk of cardiovascular-related death and all-cause death with febuxostat compared with allopurinol.⁸⁷ The agency recommended that "[h]ealth care professionals should consider this safety information when deciding whether to prescribe or continue patients on febuxostat."

On March 12, 2018, White et al. published the results of the postmarket clinical trial in *The New England Journal of Medicine* online, which demonstrated non-inferiority in terms of the primary

⁸³ *Ibid.* PDF p. 3.

⁸⁴ Food and Drug Administration. Office director memo for NDA 21-856. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_ODMemo.pdf. Accessed June 11, 2018. PDF p. 7.

⁸⁵ Food and Drug Administration. Summary review for NDA 21-856. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_SumR.pdf. Accessed June 11, 2018. PDF p. 11.

⁸⁶ Takeda Pharmaceuticals America, Inc. Label: febuxostat (ULORIC). February 2009. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021856lbl.pdf. Accessed June 11, 2018.

⁸⁷ Food and Drug Administration. Uloric (febuxostat): Drug safety communication – FDA to evaluate increased risk of heart-related death. November 15, 2017. <https://www.fda.gov/Drugs/DrugSafety/ucm584702.htm>. Updated January 22, 2018. Accessed June 11, 2018.

composite cardiovascular outcomes endpoint but higher all-cause and cardiovascular mortality in febuxostat-exposed subjects than in allopurinol-exposed subjects.⁸⁸

The Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidity (CARES) trial (NCT01101035) 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.

From April 2010 through May 2017, the CARES trial investigators enrolled 6,190 subjects (84% male and 69% white) 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.

Subjects randomly assigned to receive febuxostat started at a dosage of 40 mg once daily and increased to 80 mg once daily for the remainder of the trial if they failed to achieve an SUA of less than 6 mg/dL after two weeks of therapy. Subjects randomly assigned to receive allopurinol who had normal renal function (eCLcr ≥ 60 mL/min) started at a dosage of 300 mg of allopurinol once daily and increased the daily dose by 100 mg every month until they achieved an SUA of less than 6 mg/dL or reached the maximum dose of 600 mg once daily. Subjects randomly assigned to receive allopurinol who had impaired renal function (eCLcr < 60 mL/min) started at 200 mg once daily and increased the daily dose by 100 mg every month until they achieved an SUA of less than 6 mg/dL or reached a maximum dose of 400 mg once daily. Colchicine, naproxen or another NSAID, or prednisone for gout flare prophylaxis was administered to most subjects for the first 6 months of the study.

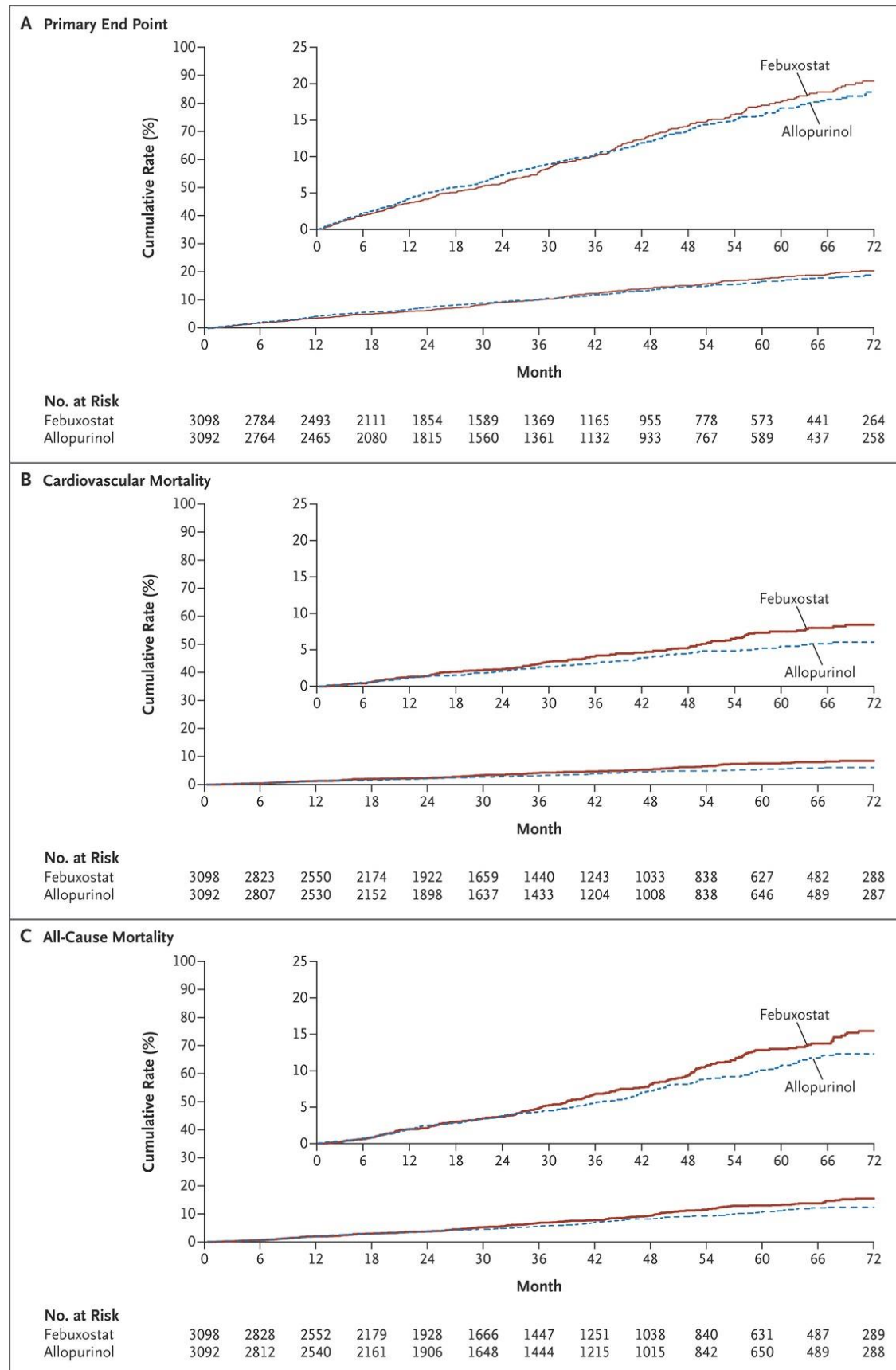
The primary composite endpoint of the trial was the first occurrence of cardiovascular death, nonfatal stroke, nonfatal myocardial infarction, or urgent revascularization for unstable angina. The secondary safety endpoints included a composite of cardiovascular death, nonfatal myocardial infarction, 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 trial was designed to accrue 624 primary events for assessing the non-inferiority of febuxostat to allopurinol with regard to cardiovascular risk, under the assumption of a true hazard ratio of 1.0 and 90% power. The median duration of follow-up was 968 days for febuxostat-exposed subjects and 942 days for allopurinol-exposed subjects.

There was no significant difference in the composite primary cardiovascular outcome (hazard ratio 1.03, 95% CI 0.87-1.23). However, there were statistically significant differences in all-cause mortality and cardiovascular mortality between the two groups. 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

⁸⁸ 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.

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; $p=0.03$). The figure below, excerpted from the White et al. paper, shows the cumulative rates for the primary endpoint, cardiovascular mortality, and all-cause mortality. The curves for cardiovascular mortality and all-cause mortality both demonstrate a progressive widening of the separation between the febuxostat and allopurinol curves over several years.

EMBARGOED UNTIL 12:01 AM EDT ON THURSDAY, JUNE 21, 2018



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 investigators reported that an outside search company (OmniTrace) identified 199 additional nonadjudicated deaths and that the excess risk of death from any cause during treatment with febuxostat persisted after incorporating these additional deaths into the analysis.

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. Low follow-up would be expected to bias towards the null hypothesis, underestimating the risk of febuxostat use.

The investigators noted that a greater proportion of febuxostat-group than allopurinol-group subjects achieved an SUA level of less than 6 mg/dL at most time points during the trial, but these differences were small. More importantly from an efficacy standpoint, the rate of gout flares among febuxostat-group subjects (0.68 flares per person-year) was not significantly different than the rate among allopurinol-group subjects (0.63 flares per person-year). The trial investigators did not report any assessment of reduction in tophus area or tophi number.

There was no significant difference in serum electrolytes, blood glucose, lipids, blood pressure, or cardiovascular medication use between the two groups.

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.

5. Recently published retrospective cohort study

In June 2018, Zhang et al. published a retrospective cohort study that used U.S. Medicare claims data from 2008 to 2013 to compare cardiovascular outcomes in gout patients age 65 or older who initiated treatment with febuxostat versus allopurinol. Using propensity-score matching with a ratio of 1 to 3, the researchers included 24,936 patients initiating febuxostat and 74,808 patients initiating allopurinol.⁸⁹ All subjects were diagnosed with gout based on an insurance claim diagnostic code, 76% were white, and 52% were male. There were no cardiovascular inclusion

⁸⁹ Zhang M, Solomon DH, Desai RJ, et al. Assessment of cardiovascular risk in older patients with gout initiating febuxostat versus allopurinol: A population-based cohort study. *Circulation*. June 2018. Epub ahead of print.

criteria. The primary outcome was a composite endpoint of hospitalization for myocardial infarction or stroke. Patient follow-up ended at the time of drug discontinuation, study conclusion, insurance disenrollment, nursing home admission, or death.

The mean follow-up time was 1.1 years among febuxostat users and 1.2 years among allopurinol users. The researchers reported no difference in the primary composite endpoint in the febuxostat patients compared with the allopurinol patients (hazard ratio 1.01, 95% CI 0.94-1.08). In a subgroup analysis of patients who were prescribed medications for over three years, the study authors reported a non-significant trend toward increased all-cause mortality among febuxostat-exposed subjects with a hazard ratio of 1.25 (95% CI 0.56-2.80).

The Zhang et al. study has numerous major methodologic limitations, including its retrospective, nonrandomized study design; lack of enrichment for patients with a history of cardiovascular disease; lack of assessment of actual use of the prescribed study medications by the patients; short mean duration of follow-up; and an inability to assess cardiovascular or other cause-specific mortality. As a result, the study offers little meaningful data for assessing the cardiovascular risks of febuxostat relative to allopurinol. The prior randomized, controlled clinical trials, particularly the CARES trial, provide the most important evidence establishing febuxostat's unsafe cardiovascular profile.⁹⁰

6. 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, and the trials demonstrated non-inferiority or superiority of febuxostat compared with allopurinol according to that surrogate biochemical marker. However, the premarket trials and the very large FDA-mandated 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.^{91,92,93,94} 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

⁹⁰ 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.

⁹¹ 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.

⁹² Schumacher HR, Becker MA, Wortmann RL, et al. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: A 28-week, phase III, randomized, double-blind, parallel-group trial. *Arthritis Care Res.* 2008;59(11):1540-1548.

⁹³ 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.

⁹⁴ 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.

concluded there were no significant differences in effectiveness between febuxostat and allopurinol.⁹⁵

Notably, in all of the premarket phase 3 trials that showed non-inferiority or superiority of febuxostat in lowering uric acid levels, allopurinol was consistently underdosed as described in the trial protocols. The FDA-approved product labeling for allopurinol since at least 2002 has recommended titrating the allopurinol dose up to 800 mg to target an SUA level of less than 6 mg/dL to reduce acute gout flares,⁹⁶ and the American College of Rheumatology and European League Against Rheumatism clinical practice guidelines also recommend allopurinol dose titration to SUA targets.^{97,98} Although claims analysis suggests that use of allopurinol at doses higher than 300 mg daily has been uncommon in practice,⁹⁹ several studies suggest that higher doses of allopurinol are safe and lead to lower SUA levels.^{100,101} The consistent under-dosing of allopurinol at 200 mg or 300 mg daily in the phase 3 febuxostat trials would tend to bias efficacy results in favor of febuxostat. Consistent with this trend, the phase 4 CARES trial that titrated both allopurinol and febuxostat to target SUA levels showed relatively small differences in the SUA-lowering effects of febuxostat and allopurinol.¹⁰²

Importantly, FDA reviewers specifically noted that interpretation of febuxostat's cardiovascular harms should be tempered by its modest surrogate benefits. For example, one FDA biostatistics team leader noted the following:

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.

⁹⁵ Tayar JH, Lopez-Olivo MA, Suarez-Almazor ME. Febuxostat for treating chronic gout. *Cochrane Database Syst Rev*. 2012;11:CD008653.

⁹⁶ Prometheus Laboratories Inc. Label: allopurinol (ZYLOPRIM). October 2003.

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/016084_S041_Zyloprim%20Tablets.pdf. Accessed June 16, 2018.

⁹⁷ Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American college of rheumatology guidelines for management of gout. Part 1: Systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care Res*. 2012;64(10):1431-1446.

⁹⁸ Richette P, Doherty M, Pascual E, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. *Ann Rheum Dis*. 2017;76(1):29-42.

⁹⁹ Sarawate CA, Patel PA, Schumacher HR, et al. Serum urate levels and gout flares: Analysis from managed care data. *J Clin Rheumatol*. 2006;12(2):61-65.

¹⁰⁰ Stamp LK, O'Donnell JL, Zhang M, et al. Using allopurinol above the dose based on creatinine clearance is effective and safe in patients with chronic gout, including those with renal impairment. *Arthritis Rheum*. 2011;63(2):412-421.

¹⁰¹ Reinders MK, Haagsma C, Jansen TLTA, et al. A randomised controlled trial on the efficacy and tolerability with dose escalation of allopurinol 300-600 mg/day versus benzbromarone 100-200 mg/day in patients with gout. *Ann Rheum Dis*. 2009;68(6):892-897.

¹⁰² 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.

Therefore, the sponsor should be asked to perform studies that demonstrate a clear clinical effect.”¹⁰³

As previously noted, in his assessment of the second complete NDA submission for febuxostat, the Director of the Division of Anesthesia, Analgesia and Rheumatology Products made the following comments in his summary review:

To approve a drug on such a surrogate when an unresolved signal of potential serious adverse [cardiovascular] effects is outstanding does not appear warranted.”¹⁰⁴

7. Conclusions

In summary, there is overwhelming 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. Rather than follow the all-important precautionary principle of public health and require an appropriately designed trial to rigorously assess the cardiovascular risks of febuxostat before approval, the FDA approved the drug and mandated a postmarket randomized controlled trial that was adequately powered to evaluate these risks. As a result, febuxostat has been aggressively marketed and prescribed to at least hundreds of thousands of patients over the past decade who were unaware of the potential dangers.

The results of the FDA-mandated postmarket trial now 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 initial NDA submission, and the appropriate course of action now is obvious. We therefore request that the FDA remove from the market all medications containing febuxostat.

C. ENVIRONMENTAL IMPACT STATEMENT

We claim categorical exclusion under 21 C.F.R. § 25.31(a) from the environmental assessment requirement. An assessment is not required because the requested action would not increase the use of the active moiety that is the subject of this petition.

¹⁰³ Food and Drug Administration. Medical review for NDA 21-856.
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_MedR_P2.pdf. Accessed June 11, 2018.
PDF p. 85.

¹⁰⁴ Food and Drug Administration. Medical review for NDA 21-856.
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_MedR_P1.pdf. Accessed June 11, 2018.
PDF p. 81.

D. ECONOMIC IMPACT

Will be submitted upon request.

E. CERTIFICATION

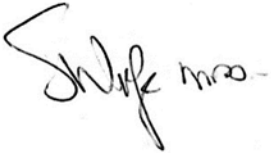
We certify that, to the best of the knowledge and belief of the undersigned, this petition includes all information and views on which this petition relies and that it includes representative data and information known to the petitioners which are unfavorable to the petition.



Max J. Romano, M.D., M.P.H.
Resident, General Preventive Medicine
Johns Hopkins Bloomberg School of Public Health



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



Sidney M. Wolfe, M.D.
Founder and Senior Adviser
Public Citizen's Health Research Group