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Re: Docket No. FDA-2018-P-2408

Dear Petitioners:

This letter responds to your citizen petition dated June 21, 2018 (Petition). The Petition asks the Food and Drug Administration (FDA or the Agency) to require removal of all drug products containing febuxostat from the market 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. FDA has carefully reviewed the Petition and all relevant information available to the Agency concerning febuxostat. Based on our review of this information and for the reasons described below, we deny your Petition. As described more fully below, FDA is approving changes to the labeling of febuxostat to address the risks of cardiovascular (CV) adverse events discussed in the Petition. In addition, as with all FDA-approved products, the Agency will continue to monitor and review available safety information as it relates to febuxostat and take any further action as appropriate.

I. BACKGROUND

A. Febuxostat

FDA approved febuxostat (new drug application (NDA) 021856) on February 13, 2009. Febuxostat, which is marketed under the trade name Uloric, is a xanthine oxidase inhibitor (XOI) that is indicated for the chronic management of hyperuricemia in patients with gout. Gout is a serious disease that can cause joint pain, urate nephropathy, and nephrolithiasis. The condition can lead to significant morbidity and negatively affect patients' quality of life. There are limited therapies available for gout; febuxostat and allopurinol are the only two FDA-approved XOIs, which have to date been considered first-line therapy for control of hyperuricemia. Both febuxostat and allopurinol are effective in reduction of serum uric acid (sUA). Reduction in sUA has been correlated with reduction in gout flares and tophi size.

B. Regulatory History of Febuxostat

The first two review cycles for febuxostat raised concerns related to CV events and death that warranted further study.¹ Upon approval, FDA required the applicant to conduct a post-marketing safety trial—Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities (CARES)—at the time of febuxostat’s approval.² CARES was a multicenter, randomized, double-blind, double-dummy, active-controlled, parallel group, non-inferiority trial to evaluate the CV safety of febuxostat versus allopurinol in gout patients with significant cardiovascular disease.

In October 2017, the applicant informed FDA of the results of the primary analysis from CARES, which showed a significant increase in CV death and all-cause death associated with febuxostat compared with allopurinol. On November 15, 2017, FDA issued a Drug Safety Communication about the risk of CV death and all-cause death based upon this preliminary information.³ The applicant submitted the final study report for the CARES trial in a supplement to NDA 021856 on January 19, 2018.

On January 11, 2019, FDA convened a joint meeting of the Arthritis Advisory Committee (AAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM AC) to discuss the results of the CARES trial.⁴ The AAC and DSaRM AC members discussed the possibility of withdrawing febuxostat from the market and voted (19 yes, 2 no, and 1 abstain) that there is a patient population for whom the benefits outweigh the risks. Members noted that there is an important role for febuxostat in the treatment of gout. Given the CV risks confirmed by CARES, most members recommended that febuxostat should be reserved for patients who cannot tolerate or have failed allopurinol.

II. LEGAL AND REGULATORY FRAMEWORK

FDA only approves drug products for marketing in the United States if those products have been shown to be safe and effective for their proposed indication(s).⁵ After an approved drug enters the marketplace, FDA may reassess its safety and consider whether changes in the available information concerning the product’s risk-benefit profile call for regulatory action.

If FDA concludes that a product’s risk-benefit profile is unfavorable, it may take steps to

¹ Additional information about the febuxostat development program and regulatory history can be found in the briefing document for the January 11, 2019, joint meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee, available at <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM629362.pdf>

² FDA, Center for Drug Evaluation and Research, Approval Letter for NDA 21-856 (February 13, 2009), at 2-3, available at https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2009/021856s000ltr.pdf.

³ See “FDA Drug Safety Communication: FDA to evaluate increased risk of heart-related death and death from all causes with the gout medicine febuxostat (Uloric),” available at <https://www.fda.gov/Drugs/DrugSafety/ucm584702.htm>.

⁴ More information about the January 11, 2019, Advisory Committee meeting can be found at <https://www.fda.gov/AdvisoryCommittees/Calendar/ucm627366.htm>

⁵ See section 505(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(b)).

withdraw approval of that application. Section 505(e)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)⁶ (21 U.S.C. 355(e)(2)) provides for FDA to withdraw the approval of a drug when consideration of new evidence of clinical experience, not contained in the NDA or not available until after the application was approved, or tests by new methods not deemed reasonably applicable when the application was approved, together with the evidence available to FDA when the application was approved, indicate that the drug “is not shown to be safe for use under the conditions of use upon the basis of which the application was approved.”

III. DISCUSSION

FDA agrees that the CARES trial and other study data demonstrate that the use of febuxostat is associated with an increased risk of cardiovascular death. However, we also have determined that there is a patient population for whom the benefits of febuxostat outweigh the risks. The Agency therefore concludes that febuxostat should not be removed from the market. Instead, as described below, FDA is approving changes to febuxostat’s labeling and intends to take other actions to address the CV safety issues supported by the results of the CARES trial.

A. Results of CARES Trial

Results from CARES show a hazard ratio (HR) of 1.03 (95% CI 0.89, 1.21) for the primary endpoint of major adverse cardiovascular events (MACE) with the use of febuxostat compared to allopurinol. Results show a significant increased risk of CV death with use of febuxostat compared to allopurinol, with a HR of 1.34 (1.03, 1.73). The cause of CV death or mechanism of action for this increased risk are not clear.⁷

B. Available Therapies for Gout

The treatment options for gout are limited. Treatment and prevention of gout involves anti-inflammatory medications such as colchicine, nonsteroidal anti-inflammatory drugs (NSAIDs), or corticosteroids for acute attacks, and urate-lowering therapies for ongoing management of hyperuricemia. Control of hyperuricemia is the foundation of management of gout. Urate-lowering therapies include the following:

- Uricosuric therapies (probenecid, sulfinpyrazone, and lesinurad⁸)
- Uricase products (pegloticase)
- XOIs (allopurinol and febuxostat)

Uricosuric and uricase products have limitations that relegate them to second or third-line therapies. Uricosuric therapies function by increasing urinary uric acid excretion and have

⁶ Section 505(e)(1) of the FD&C Act authorizes withdrawal of approval when evidence shows that the drug is unsafe for use under the conditions of use upon the basis of which the application was approved.

⁷ FDA’s complete analysis of the results of the CARES trial can be found in the briefing document for the January 11, 2019, joint meeting of the AAC and DSaRM AC, available at <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM629362.pdf>.

⁸ Note that lesinurad alone (Zurampic) and in combination with allopurinol (Duzallo), have been withdrawn from the market by the manufacturer for commercial reasons (see <https://www.duzallohcp.com> (accessed February 7, 2019)).

limitations with respect to use for patients with urolithiasis or renal impairment. Uricases function by breaking down uric acid. Because humans do not possess endogenous uricase, uricase products are highly immunogenic, often resulting in loss of efficacy and risks such as hypersensitivity reactions and anaphylaxis. Because of this, these products can only be used for limited periods of time. These products are reserved for patients with severe tophaceous gout who are refractory to conventional therapy.⁹

XOIs lower uric acid production and have to date been considered first-line therapy.¹⁰ Based upon FDA's analysis of drug utilization, allopurinol is the most widely used urate-lowering therapy in the United States with 14.9 million prescriptions dispensed, compared to 1.2 million prescriptions for febuxostat in 2017. However, allopurinol has been associated with serious skin reactions and hepatotoxicity.¹¹ Patients positive for the HLA -B*5801 allele (estimated to be up to 7% of all races but most commonly found in patients of Korean, Han Chinese, and Thai descent) are predisposed for developing allopurinol hypersensitivity syndrome (AHS).¹² Febuxostat remains the only alternative XOI to allopurinol, and therefore remains an important part of the treatment armamentarium for gout.

C. Labeling Changes and Other Actions for Febuxostat

Because of the limited treatment options available for gout and the risks associated with them, there are patients for whom the benefits of febuxostat outweigh the risks. Therefore, removal of febuxostat products from the market is not warranted at this time. Given the serious safety concerns supported by CARES, however, FDA has determined that the use of febuxostat should be limited to second line therapy for patients who cannot tolerate allopurinol or who have failed maximized allopurinol therapy. The risks of CV death must also be communicated clearly to patients and providers. Consistent with this conclusion FDA is approving the following labeling changes to address the risk of MACE in use of febuxostat:

- Approving a boxed warning in febuxostat's labeling describing the increased risk of CV death with febuxostat compared to allopurinol in CARES.
- Approving a change in indication for febuxostat to therapy for patients who have an inadequate response to a maximally titrated dose of allopurinol, who are intolerant to allopurinol, or for whom treatment with allopurinol is not advisable.
- Approving a Medication Guide to convey the CV risk information to patients who are prescribed febuxostat.

In addition:

⁹ Krystexxa (pegloticase) labeling approved on July 13, 2018, available online at https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125293s092lbl.pdf, at 2.

¹⁰ Khanna D et al, 2012, American College of Rheumatology Guidelines for Management of Gout, Part 1: Systematic Nonpharmacologic and Pharmacologic Therapeutic Approaches to Hyperuricemia, *Arthritis Care & Research* Vol. 64, No. 10, October 2012, pp 1431–1446.

¹¹ Zyloprim (allopurinol) labeling approved on December 3, 2018, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/016084s044lbl.pdf, at 4.

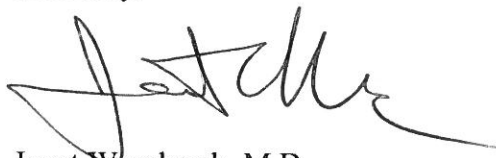
¹² Zineh I, Mummameni P, Lyndly J, La Grenade LA, Chang SH, et al. Allopurinol pharmacogenetics: assessment of potential clinical usefulness. *Pharmacogenomics* 2011;12:1741-9.

- FDA will issue an update to the November 15, 2017, Drug Safety Communication describing the outcome of FDA's postmarketing safety review of febuxostat and the labeling changes FDA is approving to address the CV safety issues confirmed by the CARES trial.
- FDA will conduct outreach to professional societies, including the American College of Rheumatology and American College of Physicians, to inform them of the changes to febuxostat's labeling.
- The applicant, pursuant to a post-marketing study commitment, will monitor the utilization of febuxostat following approval of the revised labeling.

IV. CONCLUSION

For the foregoing reasons, the Petition is denied. FDA is approving labeling changes and taking other actions as described above to address the CV risks associated with the use of febuxostat. In addition, FDA will continue to monitor available safety information as it relates to febuxostat and take any further action as is appropriate.

Sincerely,

A handwritten signature in black ink, appearing to read 'Janet Woodcock', with a long horizontal flourish extending to the right.

Janet Woodcock, M.D.

Director

Center for Drug Evaluation and Research