April 22, 2024

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Citizen Petition

HealthyWomen, the undersigned submit this petition under 21 C.F.R. § 10.30 and other pertinent regulatory and statutory provisions, including, but not limited to, 21 C.F.R. §§ 200.5 and 201.56-57 and 21 U.S.C. § 355(o)(4), to request that the Commissioner of Food and Drugs:

(1) Revise the labeling for all fenofibrate drugs currently approved by the U.S. Food and Drug Administration ("FDA" or the "Agency") to (a) remedy the widespread misimpression among healthcare professionals ("HCPs") that fenofibrates, when used alone or in combination with statins, reduce cardiovascular risk, and the resulting pervasive, improper utilization of fenofibrates, and (b) incorporate important new, related information from the recently published PROMINENT Study,[1] and

(2) Take further actions to ensure this information is expeditiously communicated to HCPs and patients (*i.e.*, through Dear Health Care Provider Letters ("DHCP Letters") and Drug Safety Communications ("DSCs")).

Significantly, the data from the recent PROMINENT Study settled a scientific issue that has been pending for years – whether fibrates have cardiovascular benefits. As described below, all of the studies examining this question have answered it with a resounding "no." Fibrates did not meet the primary endpoint for cardiovascular benefit when used as a monotherapy (FIELD

[1] *See* A.D. Pradhan et al., Triglyceride Lowering with Pemafibrate to Reduce Cardiovascular Risk, NEJM 387:1923 (2022) ("PROMINENT Study").

Study),[2] or when used in combination with statins (ACCORD Lipid Study),[3] and pemafibrate also did not show any cardiovascular benefit, even when used in combination with statins in a subpopulation that experts initially thought was more likely to benefit, namely patients with high triglyceride ("TG") and low high-density lipoprotein cholesterol ("HDL-C") (PROMINENT Study).[4]

Indeed, taking the PROMINENT Study into account, the recent 2023 AHA/ACC Guidelines make clear, in particular, that fenofibrates have no cardiovascular benefit over and above statins, stating bluntly that: "In patients with [chronic coronary disease] receiving statin therapy" adding fenofibrate is "not beneficial in reducing cardiovascular risks."[5] The guidelines also unambiguously conclude that fenofibrates "should only be considered for severe hypertriglyceridemia (triglycerides ≥500 mg/dL) to reduce the risk of pancreatitis."[6]

We acknowledge and applaud the substantial actions FDA has previously taken to debunk the presumed association between fenofibrates and cardiovascular benefit. For example, as discussed in detail below, after the FIELD Study and the ACCORD Lipid Study, FDA revised fenofibrate product labeling, to add or modify limitations of use and to update the warnings and precautions – to capture the studies' results.[7] FDA also convened an Advisory Committee in 2011 to discuss the findings of the ACCORD Lipid Study as they relate to the safety and effectiveness of Trilipix.[8] In addition, in 2016, FDA announced that it had taken the scientifically justified step of withdrawing its approval of the indication related to statin coadministration for fenofibric acid delayed-release capsules – finding that the "coadministration with statins no longer outweigh[s] the risks."[9]

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[2] The FIELD Study Investigators, Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus ("FIELD Study"): randomised controlled trial, The Lancet 366 (Nov. 26, 2005).

[3] (combination therapy of statin and fenofibrate did not reduce cardiovascular risk in patients with type 2 diabetes compared to statins alone). The ACCORD trial had multiple objectives, with the ACCORD Lipid component relevant to the discussion here.

[4] *See* PROMINENT Study.

[5] 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines, Circulation. 2023;148:e00–e00 (July 2023), DOI: 10.1161/CIR.0000000000001168, at e29.

[6] *Id.* at e34.

[7] *See, e.g.*, FDA, NDA 21656/S-004, S-011, Tricor (fenofibrate) Approval Letter (Sept. 10, 2007); FDA, NDA 22224/S-005, S-006, Trilipix (fenofibric acid) Approval Letter (Sept. 30, 2011).

[8] FDA, Endocrinologic and Metabolic Drugs Advisory Committee; Notice of Meeting, 76 Fed. Reg. 23324 (Mar. 26, 2011).

[9] Notice, AbbVie Inc. et al; Withdrawal of Approval of Indications Related to the Coadministration With Statins in Applications for Niacin Extended-Release Tablets and Fenofibric Acid Delayed-Release Capsules, 81 Fed. Reg. 22612, 22613 (Apr. 18, 2016).

Yet, recent surveys of cardiologists, primary care physicians ("PCPs") and pharmacists indicate that there remains marked confusion over whether fenofibrates reduce cardiovascular risk. Indeed, over half of the cardiologists and PCPs who were surveyed in a 2021 Harris Poll, believed that fenofibrates reduce the risk of cardiovascular disease for both men and women.[10] Moreover, the same Harris Poll showed that 38% of the cardiologists, 42% of the PCPs, and 42% of the pharmacists surveyed believed that FDA had approved taking fenofibrates in combination with statins; and only 15% of the cardiologists, 14% of the PCPs, and 14% of the pharmacists knew that the approval has been withdrawn.[11] Similarly, a 2023 InCrowd survey showed that 58% of the HCPs interviewed believed that fenofibrates reduce the risk of cardiovascular disease and 65% believed that when fenofibrates are taken with a statin, they reduce the risk of cardiovascular disease above and beyond the statin alone.[12]

The Centers for Disease Control and Prevention ("CDC") reports that over 60 million women (44%) in the United States are living with some form of heart disease, and that heart disease is the leading cause of death in women in the U.S.[13] According to the CDC, in 2021, heart disease was responsible for the deaths of 310,661 women—or about 1 in every 5 female deaths.[14] Despite the prevalence of heart disease in women, research shows that women continue to be undertreated for heart disease, compared to men.[15]

The pervasive misperceptions about, and misuse of, fenofibrates mean that women, as well as men, are foregoing safe and effective therapies that work. In other words, neither women or men are being adequately treated for residual cardiovascular risk, offered the full spectrum of available and appropriate interventions, and they are being exposed to unnecessary fenofibrate-related risks. Payors are also incurring unnecessary costs. FDA-approved labeling is the "primary tool for communicating drug information to healthcare professionals,"[16] and we urge FDA to update the labeling for fenofibrates as quickly as possible and to reach out more broadly to HCPs and patients, with DHCP Letters and DSCs. The recent results from PROMINENT prompt further action now.

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[10] Harris Poll data, June 2021. D/E Letters indicate significant differences between segments at 95% Confidence Level.

[11] *See id.*

[12] InCrowd Survey 2023.

[13] CDC, Heart Disease, https://www.cdc.gov/heartdisease/women.htm

[14] *See id.*

[15] The slowly evolving truth about heart disease and women, American Heart Association News, Feb. 9, 2024, https://www.heart.org/en/news/2024/02/09/the-slowly-evolving-truth-about-heart-disease-and-women#:~:text=Research%20shows%20women%20continue%20to,for%20heart%20attacks%20and%20strokes

[16] Frequently Asked Questions About Labeling for Prescription Medicines, *available at* FDA, https://www.fda.gov/drugs/fdas-labeling-resources-human-prescription-drugs/frequently-asked-questions-about-labeling-prescription-medicines.

A. Action Requested

We respectfully request that FDA:

1. Require the following changes be made to the labeling for all FDA-approved fenofibrates[17,18]

    a. Revise the Limitation of Use statement to clarify the lack of any cardiovascular benefit when fenofibrates are used alone or in combination with a statin, including in patients with high TG and low HDL-C levels.

    b. Revise Section 5.1, Mortality and Coronary Heart Disease Morbidity, to incorporate results from the recently published PROMINENT Study; and

    c. Revise the warnings in Section 5.3 Myopathy and Rhabdomyolysis and Section 5.10 Venothromboembolic Disease to reflect the results from the PROMINENT Study.

2. Require the holders of approved marketing applications for fenofibrate products to issue DHCP letters conveying this important information.

3. Issue a DSC highlighting the results of the PROMINENT Study and update the DSC once the labeling changes have been implemented.

B. Statement of Grounds

1. *Background*

Fenofibrate is a member of the class of fibric acid derivatives. These drugs are peroxisome proliferator-activated receptor ("PPAR") agonists, and they effect a number of lipid profile changes.[19] FDA first approved fenofibrate in 1993, Lipidil, under NDA 19304, as an adjunctive therapy to diet for the treatment of adult patients with very high elevations of serum triglyceride levels (Types IV and V hyperlipidemia), who are at risk for pancreatitis and who do not respond

[17] FDA-approved fenofibrates include the following drugs approved under New Drug Applications ("NDAs"), as well as the Abbreviated New Drug Applications ("ANDAs") referencing such drugs: Antara (Micronized) (fenofibrate); Fenoglide (fenofibrate); Fibricor (fenofibric acid); Lipidil (fenofibrate); Lipofen (fenofibrate); Tricor (fenofibrate); Triglide (fenofibrate); and Trilipix (fenofibric acid). The NDA for Tricor (Micronized) (fenofibrate) was voluntarily withdrawn. *See* Notice, Hospira, Inc. et al.; Withdrawal of Approval of 44 New Drug Applications and 158 Abbreviated New Drug Applications, 81 Fed. Reg. 68427 (Oct. 4, 2016). There are no approved ANDAs referencing Tricor (Miconized). We found no formal withdrawal of approval for Lipidil (fenofibrate), though it does not appear there have been any updates to its labeling since 2002. *See* Drugs@FDA, Lipidil.

[18] We recognize that requiring labeling changes can involve different mechanisms for NDA and ANDA holders.

[19] *See* FDA, NDA 19304/S-005, Tricor (fenofibrate) Medical Review (Mar. 19, 2002).

adequately to a determined dietary effort to control them.[20] While fenofibrates continue to have limited utility in the treatment of patients with severe hypertriglyceridemia as well as primary hypercholesterolemia and mixed dyslipidemia which are not at issue here, they have no value in reducing cardiovascular disease risk.

As acknowledged by FDA with the approval of the first fenofibrate (Lipidil), and as reflected in the drug's labeling (specifically, the Warnings section), fenofibrate's "effect on coronary heart disease morbidity and mortality and non-cardiovascular mortality has not been established."[21] Nevertheless, even as FDA approved additional fenofibrate products,[22] clinical evidence began to emerge questioning whether these drugs' lipid-lowering effects would ultimately translate into a benefit of decreased cardiovascular risk. In November 2005, the results from the FIELD Study were released. FIELD, a randomized, blinded placebo-controlled trial, assessed the effect of fenofibrate monotherapy on cardiovascular disease events in patients with type 2 diabetes. Fenofibrate did not significantly reduce the risk of the primary outcome of coronary events. The investigators, however, hypothesized that the higher rate of statin therapy in patients allocated to the placebo group might have masked a moderate treatment benefit.[23]

Based on the results of the FIELD Study, which is the largest study of fibrate use in women with diabetes, FDA updated fenofibrate labeling. These updates revised the statement that the effect of the drug on coronary heart disease morbidity and mortality has not been established to instead recognize that "[f]enofibrate was not shown to reduce coronary heart disease morbidity and mortality in a large, randomized controlled trial of patients with type 2 diabetes mellitus," and incorporated that statement into the Indications and Usage section of the labeling.[24] FDA similarly incorporated the FIELD Study results into the Warnings section of labeling, accompanying the existing descriptions of "adverse findings" in clinical trials with other fibrate drugs that "may also apply" to fenofibrate.[25]

On December 15, 2008, FDA approved the fenofibrate, Trilipix (f enofibric acid, NDA 22224) with an additional indication for co-administration with statin to reduce TG and increase HDL-C in patients with mixed dyslipidemia and CHD or a CHD risk equivalent who are on optimal statin therapy to achieve their LDL-C goal.[26] In connection with its evaluation of the drug's

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[20] *See* FDA, NDA 19304, Lipidil (fenofibrate) Approval Letter (Dec. 31, 1993); *see also* FDA, NDA 19034, Lipidil (fenofibrate) Action Package. The labeling further explained that "Patients who present such risk typically have serum triglycerides over 2000 mg/dL and have elevations of VLDL-cholesterol as well as fasting chylomicrons (Type V hyperlipidemia)."

[21] *See* FDA, NDA 19034, Lipidil (fenofibrate) Action Package.

[22] *See supra*, n.15.

[23] *See* The FIELD Study Investigators, Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial, The Lancet 366 (Nov. 26, 2005).

[24] *Compare* Tricor (NDA 19304) United States Prescribing Information ("USPI") (Apr. 11, 2000) *with* Fenoglide (NDA 22118) USPI (Aug. 10, 2007). *See also* FDA, NDA 22118, Fenoglide (fenofibrate) Medical Review (Aug. 9, 2007) (recommending incorporation of the FIELD Study into the labeling).

[25] *See, e.g.*, FDA, NDA 21656/S-004, S-011, Tricor (fenofibrate) Approval Letter (Sept. 10, 2007).

[26] FDA, NDA 22224, Trilipix (fenofibric acid) Approval Letter (Dec. 15, 2008).

benefit-risk profile, FDA acknowledged that it had previously recommended against co-administration with statins given concerns with increased rhabdomyolysis risks. FDA nevertheless concluded that those risks were more closely tied to another fibrate, gemfibrozil. On effectiveness, the application contained no clinical evidence to establish the cardiovascular benefits of the Trilipix-induced lipid reductions, let alone in combination with statins. Rather, as FDA later commented, historically, it had approved applications based on favorable changes in lipid profile, with the assumption that these changes would translate into beneficial clinical outcomes.[27] Accordingly, in addition to the FIELD Study-related indication limitation, the drug's indication included a further limitation of use: "No incremental benefit of Trilipix on cardiovascular morbidity and mortality over and above that demonstrated for statin monotherapy has been established."[28]

The ACCORD Lipid Study sought to address the clinical gap left by the FIELD Study – whether changes in lipid profile induced by fenofibrate add-on therapy would yield an incremental cardiovascular benefit for statin-treated patients. The study compared the impact of concomitant statin and fenofibrate therapy and statin monotherapy on the reduction of cardiovascular disease risk in patients with type 2 diabetes at high risk for cardiovascular disease. The ACCORD Lipid Study found that the combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke, as compared to simvastatin alone.[29] In addition, while the clinical significance remains unclear, the hazard ratio for MACE (or Major Adverse Cardiovascular Event, a composite endpoint frequently used in cardiovascular research) in women receiving combination therapy versus statin monotherapy in the ACCORD Lipid Study was 1.38 (95% CI 0.98-1.94) (interaction p=0.01), which was higher than the male population in this study.[30] However, the investigators left open the possibility that patients who had TG levels in the highest third and HDL cholesterol in the lowest third could potentially benefit from the addition of fenofibrate.[30]

Following release of the ACCORD Lipid Study results, FDA convened an Advisory Committee on May 19, 2011. A plurality of members voted in favor of leaving in place Trilipix's statin co-administration indication with modified labeling, though four members voted for withdrawal. While there was general consensus that the ACCORD Lipid Study did not demonstrate a significant benefit of statin and fibrate co-administration, certain members expressed concerns that the study was not designed to assess cardiovascular benefits specifically in patients with

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[27] *See* FDA Briefing Information for the October 16, 2013 Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee ("Oct. 2013 AC FDA Briefing Package").

[28] Trilipix (NDA 22224) USPI (Dec. 15, 2008); *see also* FDA, NDA 22224, Trilipix (fenofibric acid), Summary Review for Regulatory Action (Dec. 15, 2008) ("The Trilipix labeling will include a disclaimer that the incremental benefit of Trilipix on cardiovascular morbidity and mortality when added to stating therapy is unknown.").

[29] The ACCORD Study Group, Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus, NEJM 362:1563-1574 (Apr. 29, 2010).

[30] *Id*. ("Our subgroup results and those of these previous trials support the view that the addition of fenofibrate to a statin may benefit patients with type 2 diabetes who have substantial dyslipidemia.").

high TG levels and low HDL-C levels, and thus could not fully evaluate the benefits of the add-on of fenofibrate to statins in patients with residual dyslipidemia. Indeed, much of the discussion was devoted to this topic, with FDA even including a question specific to the subgroup analysis.[31] In addition, all 13 members voted in favor of requiring the Trilipix applicant to conduct a clinical trial designed "to test the hypothesis that, in high-risk men and women at LDL-C goal on a statin with residually high TG and low HDL-C, add-on therapy with Trilipix versus placebo significantly lowers the risk of MACE [major adverse cardiovascular events]."[32]

FDA agreed with the plurality's recommendation to incorporate the principal findings from the ACCORD Lipid Study into fenofibrate labeling. Following the Advisory Committee meeting, FDA initiated a safety labeling change pursuant to section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act ("FD&C Act").[33] Trilipix's new labeling, approved in NDA 22224/S-005 on September 30, 2011, incorporated data and information from the ACCORD Lipid Study into Section 5.9 Mortality and Coronary Heart Disease Morbidity. Additionally, the General Considerations for Use were merged under the Important Limitations of Use, which read:

> No incremental benefit of Trilipix on cardiovascular morbidity and mortality over and above that demonstrated for statin monotherapy has been established. Fenofibrate at a dose equivalent to 135 mg of Trilipix was not shown to reduce coronary heart disease morbidity and mortality in 2 large, randomized controlled trials of patients with type 2 diabetes mellitus.[34]

FDA also issued a postmarketing requirement ("PMR") for a clinical trial under section 505(o)(3) of the FD&C Act, consistent with the recommendations of the Committee.[35,36]

In addition, FDA issued a Drug Safety Communication and accompanying Drug Safety podcast in November 2011 that among other things noted that, consistent with the Important Limitations of Use, "[f]enofibrate at a dose equivalent to 135 mg of Trilipix was not shown to reduce coronary heart disease morbidity and mortality in patients in two large randomized controlled trials of patients with type 2 diabetes mellitus."[37] Further, FDA updated the labeling of all

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[31] Questions to the Endocrinologic and Metabolic Drugs Advisory Committee (May 19, 2011).

[32] Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee (May 19, 2011).

[33] *See* FDA, NDA 22224/S-005, S-006, Trilipix (fenofibric acid) Approval Letter (Sept. 30, 2011) (referring to a July 6, 2011 correspondence "notifying you [the NDA holder] of new safety information that we believe should be included in the labeling for Trilipix (fenofibric acid) under Section 505(o)(4) of the FDCA").

[34] Trilipix (NDA 22224) USPI (Sept. 30, 2011).

[35] FDA, NDA 22224/S-005, S-006, Trilipix (fenofibric acid) Approval Letter (Sept. 30, 2011).

[36] The status of the PMR was posted until approximately 2016 (*i.e.*, around the time when FDA withdrew the statin co-administration indication), and is no longer listed in FDA's public databases. It does not appear that the study was ever completed.

[37] FDA Drug Safety Communication: Review update of Trilipix (fenofibric acid) and the ACCORD Lipid trial, *available at* https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-review-update-trilipix-fenofibric-acid-and-accord-lipid-trial; *see also* FDA Drug Safety Podcast for Healthcare Professionals:

fenofibrate products (including Trilipix) to update the Warnings and Precautions section of the labeling based on the ACCORD Lipid Study.[38]

On October 16, 2013, FDA also convened another Advisory Committee to discuss a pending supplemental application for another product (icosapent ethyl) as an add-on to statin therapy. Although the Committee was considering an application for a different drug, it confronted the larger question as to whether changes in certain lipid profiles (in particular, TGs) translate into a clinical benefit, which necessarily implicated fenofibrates. For example, during FDA's presentation, it explained that "[r]ecent cardiovascular outcome trials with fenofibrates and niacin call into question whether targeting lipids and lipoproteins other than LDL yield incremental cardiovascular benefit in the setting of contemporary statin treatment."[39] One of the voting members, Dr. Everett, observed that "the field of adjunctive agents is littered with failures. … The fibrates are another."[40] The Committee ultimately voted against approval in the absence of a study that measured the drug's impact on cardiovascular risk (and not just on its lipid-lowering effects). As observed by several members, "most contemporary evidence has not supported the hypothesis that lowering triglycerides leads to CV benefit."[41] Notwithstanding their vote, both the Committee and FDA acknowledged the potential cardiovascular benefit of TG-lowering agents in patients with high TG and low HDL-C levels.[42]

Shortly thereafter, FDA withdrew approval of Trilipix's statin co-administration indication.[43] As explained in a subsequently issued Federal Register notice, FDA had determined that the totality of the scientific evidence no longer supported the conclusion that a drug-induced reduction in TG levels and/or increase in HDL-C levels in statin-treated patients resulted in a reduction in the risk of cardiovascular disease events. Accordingly, FDA concluded that "the benefits for coadministration with statins no longer outweigh the risks, and the approval for th[e] indication should be withdrawn."[44] In addition to removing the indication from the labeling, other changes

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Review update of Trilipix (fenofibric acid) and the ACCORD Lipid trial (Nov. 9, 2011), *available at* http://wayback.archive-it.org/7993/20170113093238/http:/www.fda.gov/Drugs/DrugSafety/DrugSafetyPodcasts/ucm279570.htm.

[38] *See, e.g.*, FDA, NDA 22224/S-005, S-006, Trilipix (fenofibric acid) Approval Letter (Sept. 30, 2011); FDA, NDA 21656/S-023, Tricor (fenofibrate) Approval Letter (Feb. 5, 2013).

[39] Transcript from the Endocrinologic and Metabolic Drugs Advisory Committee Meeting (Oct. 16, 2013) at 157 ("Oct. 2013 AC Tr.").

[40] *Id*. at 264-65.

[41] Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee Meeting (Oct. 16, 2013); *see also* Oct. 2013 AC Tr. at 254 (As commented by voting member, Dr. Seely, "I've seen no data that this [*i.e.*, lowered TGs] will translate into a meaningful reduction in cardiovascular risk among the target population.").

[42] Oct. 2013 AC FDA Briefing Package (Subgroup analyses from ACCORD, along with two trials evaluating other lipid-lowering drugs (EPA in JELIS and Niacin in AIM-HIGH), suggested that patients with elevated TG and low HDL-C "might experience a greater potential treatment benefit with additional lipid modifiers to a statin regimen."); *see also* Oct. 2013 AC Tr. at 283.

[43] FDA, NDA 22224/S-011, Trilipix (fenofibric acid) Approval Letter (Apr. 27, 2015) (removing the indication and related labeling statements).

[44] 81 Fed. Reg. at 22613; FDA concurrently announced withdrawal of approval of the statin co-administration indication for Niaspan (niacin). *See id.*

were implemented. These included revisions to the Limitations of Use to omit the lack of any established incremental benefit over statins as well as removal of certain statin-related warning information.

Notwithstanding this history, the belief that statin-treated patients may benefit from fenofibrate therapy persists. Indeed, one report concluded that 20% of news and biomedical journal articles published on the ACCORD Lipid Study described fenofibrate as effective; what is more, 50% of news and 67% of biomedical journals that included treatment recommendations supported continued fenofibrate use.[45] Moreover, with the Trilipix PMR study never completed, the view that patients with elevated TG and low HDL-C levels might benefit from the addition of a lipid modifier to statin treatment has become particularly entrenched.

The PROMINENT Study sought to fill the gap left open by the unfulfilled Trilipix PMR and directly addressed the subpopulation hypothesis—and found no additional cardiovascular benefit with fibrate add-on therapy.[46] PROMINENT, a multinational, double-blind, randomized, controlled trial, compared patients with type 2 diabetes, mild-to-moderate hypertriglyceridemia (TG of 200 to 499 mg/dL), and HDL-C below 40 mg/dL, who received pemafibrate or a matching placebo, with 95.7% of patients receiving statin therapy at baseline. Pemafibrate is chemically, pharmacologically, and clinically similar to fenofibrate.[47]

Consistent with prior trials,[48] while pemafibrate significantly decreased TGs, there was no difference in the incidence of cardiovascular events in patients receiving pemafibrate versus the placebo. PROMINENT found that not only did pemafibrate fail to offer any additional clinical benefit but also there were increases in the incidence of venous thromboembolism in patients in the pemafibrate arm as compared to the placebo arm. These results are consistent with the

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[45] N.S. Downing et al., Disseminating Evidence from a Landmark Trial: Cross-Sectional Analysis of Descriptions and Interpretations of the ACCORD-Lipid Trial in the News and Biomedical Literature, JAMA Intern. Med. 174(7):1176 (2014).

[46] *See* A.D. Pradhan et al., Triglyceride Lowering with Pemafibrate to Reduce Cardiovascular Risk, NEJM 387:1923 (2022).

[47] Pemafibrate, included in the same ATC classification family, C10AB, as fenofibrate, shares a similar phenoxy acid moiety as other fibrates, but with unique benzoxazole and phenoxyalkyl chemical groups, resulting in enhanced PPARα activity and selectivity relative to fenofibrate and other fibrates. Pemafibrate and fenofibrate exhibit similar *in vitro* and *in vivo* activities associated with PPARα agonism, such as increased expression of genes involved in fatty acid oxidation. Although pemafibrate has shown increased potency relative to fenofibrate, the TG lowering effect of pemafibrate, a reduction of 26% (at the dose used in the PROMINENT trial), is comparable to fenofibrate (approximately 21-23% in the ACCORD Lipid trial). *See* Yamazaki Y et al., Design and synthesis of highly potent and selective human peroxisome proliferator-activated receptor alpha agonists. Bioorg Med Chem Lett. 2007;17:4689–93; Yamashita S et al., Pemafibrate, a new selective PPARα modulator: Drug concept and its clinical applications for dyslipidemia and metabolic diseases. Curr Atherosclerosis Rep 22(5), 2020. Similar TG-lowering effects were also seen in a 12-week study design. *Compare* Trilipix (NDA 22224) USPI, Section 14 (Sept. 5, 2012) *with* Yamashita S. et al., Efficacy and Safety of Pemafibrate, a Novel Selective Peroxisome Proliferator-Activated Receptor Modulator (SPPARM): Pooled Analysis of Phase 2 and 3 Studies in Dyslipidemic Patients with or without Statin Combination. Int. J. Mol. Sci. 20:5537 (2019).

[48] Although FIELD was ostensibly a monotherapy trial, as explained by the PROMINENT investigators, the disproportionate drop-in to statin therapy in the placebo may explain the study's neutral finding.

FIELD Study and the Coronary Drug Project.[49] They are also consistent with recently reported analyses of observational data. For example, the World Health Organization pharmacovigilance database, Vigibase, reported that fibrates, and especially fenofibrates, were significantly associated with an increased risk of venous thromboembolism (ROR 1.55; CI 1.44—1.67)). Similarly, a multivariate analysis of the Caen University Hospital medical information database showed a significant association between fenofibrates and a higher risk of venous thromboembolism events that required hospitalization (OR 3.67, CI 1.82-7.37, p = 0.0003).[50]

Notwithstanding the repeated failed clinical outcome trials evaluating fenofibrates and cardiovascular outcomes, there remains a continued misimpression that fenofibrates, alone, or in combination with a statin reduce cardiovascular risk. This results not only in misdirected and inappropriate care, but also in a massive waste of scarce resources by federal and commercial health care programs paying for non-effective treatment. The Symphony METYS database reports that while fibrate utilization has come down somewhat since 2015 when the FDA removed the statin co-administration from the labeling of fenofibric acid delayed-released capsules, there were still over 11 million prescriptions written for fenofibrates in 2023, accounting for over $1.5 billion in expense.[51] Moreover, today, approximately 1.7 million patients are being inappropriately treated with fenofibrates, of which approximately 40% are women.[52] While some of those prescriptions were no doubt appropriate for the patient receiving treatment, many are foregoing effective treatment to reduce their cardiovascular risk. Regardless, the result is an entirely preventable failure to reduce the number of cardiovascular events experienced by these patients. Moreover, the costs of treating the cardiovascular events that could have been avoided is staggering—likely over one billion dollars wasted, year after year, due to inappropriate fibrate prescriptions.[53]

Looking at the totality of the data generated through the years and given the latest data set from the PROMINENT Study (as described below), FDA action is critical. In addition, a course-correction in prescriber behavior would have the added benefit of reducing the costs of preventable cardiovascular events, particularly now when the Medicare Trust funds are at risk of running out of funds and payers are contemplating rationing care.

2. *Legal Standard*

[49] *See* Trilipix (NDA 22224) UPSI, § 5.10 (June 3, 2021).

[50] Dolladille C, et al. Association between venous thromboembolism events and fibrates: A comparative study. Therapie 2019;74:421-30.

[51] [Database footnote.] This estimate is calculated using product wholesale acquisition cost (WAC), and does not account for any manufacturer discounts and rebates related to such products.

[52] Symphony METYS database..

[53] *See* C.G. Derington, The potential population health impact of REDUCE-IT eligible US adults with Icosapent Ethyl, Am. J. Prev. Cardiol., (Apr. 28, 2022) (exploring population health impacts of treating patients with icosapent ethyl).

The primary purpose of FDA-approved labeling is "to provide practitioners with the essential information they need to prescribe the drug safely and effectively for the care of patients."[54] This includes (1) limitations regarding the approved uses of the drug in the Indications and Usage Section[55] and (2) risk information in the Warnings and Precautions Section.[56]

- **Limitations in the Indications and Usage Section (21 C.F.R. § 201.57(c)(2))** – FDA recognizes that when there exists "a common belief that a drug may be effective for a certain use or [] there is a common use of the drug for a condition," but the evidence shows that the drug is "ineffective" or "that the therapeutic benefits of the product do not generally outweigh its risks" — the labeling may be required to state there is a lack of evidence that the drug is safe or effective in that condition.[57]
- **Warnings and Precautions Section (21 C.F.R. § 201.57(c)(6))** – According to FDA regulations, this section provides information on "clinically significant adverse reactions" with, at minimum, "reasonable evidence of causal association."[58] FDA has adopted a standard to prevent "overwarning" to avoid "deter[ring] appropriate use"[59] or "overshadow[ing] more important warnings," but a causal relationship between the drug and the adverse event need not be definitively established.[60] This section, too, can include information pertaining to diseases or conditions for which the drug is not approved, such as when "the drug is commonly prescribed for a disease or condition and such usage is associated with a clinically significant risk or hazard."[61]

Although applicants have an ongoing obligation to ensure their drug labeling is not inaccurate, false, or misleading,[62] FDA may also initiate certain labeling changes. Specifically, section 505(o)(4) of the FD&C Act authorizes FDA to implement safety labeling changes if FDA becomes aware of "new information, including any *new safety information* or *information*

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[54] Final Rule, Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3921, 3968 (Jan. 24, 2006) (internal quotation marks and citation omitted).
[55] *See* 21 C.F.R. § 201.57(c)(2)(i).
[56] *See id*. § 201.57(c)(6)(i).
[57] *Id.* § 201.57(c)(2)(ii).
[58] *Id*. § 201.57(c)(6)(i); *see also* Oct. 2013 AC Tr. at 291 ("[T]alking about safety, the data about fibrates and statin interactions … [is] very, very real. … And every EMR [electronic medical record] sets off alarms when you want to use a statin with a fibrate.").
[59] Final Rule, Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. 49603, 49605-06 (Aug. 22, 2008).
[60] 21 C.F.R. § 201.57(c)(6)(i); *see also* FDA Guidance for Industry, *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products—Content and Format* (Oct. 2011) ("W&P Guidance").
[61] 21 C.F.R. § 201.57(c)(6)(i).
[62] *Id*. § 201.56(a)(2).

related to reduced effectiveness, that the Secretary determines should be included in the labeling of the drug."[63]

3. *Requested Labeling Changes*

We urge FDA to update the labeling of fenofibrates to (a) remedy the widespread misimpression among HCPs that fenofibrates, when used alone or in combination with statins, reduce cardiovascular risk, and the resulting, entrenched improper prescribing of fenofibrates for this use, and (b) incorporate important new, related information from the recently published PROMINENT Study. Indeed, FDA has a long history of updating fenofibrate labeling in response to multicenter, adequately-controlled clinical trials demonstrating that fenofibrate therapy did not result in cardiovascular benefits. Significant labeling changes were made after the FIELD Study and the ACCORD Lipid Study, with revisions to both the Indications and Usage and Warnings and Precautions sections (and their pre-Physician Labeling Rule correlates).

Moreover, the PROMINENT Study constitutes "new safety information or information related to reduced effectiveness," with the results providing critical, new information that implicates the benefit-risk profile of fenofibrates and is essential to fenofibrate prescribing decisions.[64] *First*, the PROMINENT trial squarely addressed the question of whether statin-treated patients with high TG and low HDL-C patients would benefit from addition of fibrate add-on therapy—and found that they would not. *Second*, while offering no incremental cardiovascular benefit, adding fibrate to statin therapy does pose risks, with the PROMINENT trial observing an increased risk in venous thromboembolism, similar to those seen in the FIELD study with fenofibrate and the Coronary Drug Project with clofibrate. This information, pertaining to an unapproved, but often-prescribed, use, both clarifies the absence of any cardiovascular benefit and contextualizes risk information, warranting labeling revisions to ensure that healthcare providers can make informed treatment decisions and patients are not left untreated for residual cardiovascular risk and receive

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[63] *See* 21 U.S.C. § 355(o)(4)(A) (emphasis added). The Substance Use-Disorder Prevention that Promotes Recovery and Treatment for Patients and Communities Act amended section 355(o)(4) to authorize FDA to initiate safety labeling changes based on new information related to reduced effectiveness. *See* Pub. L. 115-271 § 3401 (2018). *See also* 21 U.S.C. § 355-1(b)(3) for the definition of "new safety information."

[64] Although the PROMINENT Study evaluated an investigational pemafibrate, the findings are applicable to fenofibrates given their chemical, pharmacological, and clinical similarity (*see supra*, n.45). FDA has long recognized the relevance of data generated with related products to safety and effectiveness as well as labeling decisions. *See, e.g.*, FDA Final Rule, New Drug and Antibiotic Regulations, 50 Fed. Reg. 7452, 7460-7461 (Feb. 22, 1985) (explaining that FDA did not believe that information about "related drugs, such as epidemiologic data, can be ignored in evaluating a new drug" and that "[s]uch information may be relevant to labeling and may help focus the evaluation of the data submitted"); *see also* 21 C.F.R. § 201.57(c)(7)(i) (requiring the listing of adverse reactions that occur with the drug "and with drugs in the same pharmacologically active and chemically related class"). Indeed, FDA already has incorporated information generated with other fibrates—specifically, clofibrate and gemfibrozil—into fenofibrate labeling given their "similarities" to the labeled drug, reflecting FDA's determination that such information is relevant to fenofibrate prescribing decisions. The fact that pemafibrate is not U.S.-approved does not change this analysis, and FDA has included references to non-U.S. approved drugs in product labeling. *See, e.g.*, Cosentyx (Biologics License Application ("BLA") 125504) USPI (Jan. 1, 2015) (referring to non-U.S. approved vaccines).

the care they need. Like its predecessor FIELD and ACCORD Lipid Studies, the PROMINENT Study warrants revised labeling.

The specific labeling changes requested follow.

- **Indications and Usage, Limitations of Use, Section 1** – While Trilipix's labeling previously bore a limitation of use pertaining to the lack of an established incremental benefit of fenofibrate statin add-on therapy, that limitation was removed when FDA withdrew approval of the statin co-administration indication. Notwithstanding FDA's withdrawal of this indication, however, there remains a persistent belief that fenofibrate add-on therapy can reduce cardiovascular risk—particularly in patients with high TG levels and low HDL-C levels. This is not entirely surprising. As mentioned, scientific experts have given credence to the possibility that statin add-on therapy may benefit patients with type 2 diabetes who have substantial dyslipidemia. This has been evidenced by the prescribing habits captured in the 2021 Harris Poll data, with healthcare providers continuing to use fenofibrates in combination with statins.[65]

  The PROMINENT trial, however, has laid this theory to rest. The trial showed both that fibrate co-administration is ineffective for reducing cardiovascular benefit and that, despite the absence of any benefit, it poses risks (*e.g.*, venous thromboembolism). Not to mention, patients treated with fibrates in addition to statins may forgo the use of other add-on therapies that are safe and effective treatments for their conditions. In other words, the PROMINENT trial confirmed FDA's prior conclusion that "the benefits for co-administration with statins no longer outweigh the risks."[66] Nonetheless, as mentioned, HCPs continue to be under the misimpression that fenofibrates, alone, or in combination with a statin reduce cardiovascular risk.[67] Notably, as captured in post-PROMINENT Study September 2023 data, cardiologists—who are the most familiar with the state of the science, including the series of failed cardiovascular outcome studies—write only 7% of total fenofibrate prescriptions.[68] This figure underscores the importance of revising the labeling to communicate this important information on fenofibrate's benefit-risk profile to all prescribers, including general practitioners, family physicians, and internal medicine physicians.

  Accordingly, we request that FDA revise the Limitations of Use, consistent with its authority in 21 C.F.R. § 201.57(c)(2)(ii) – by adding the underlined language below:[69]

[65] Harris Poll data, June 2021. D/E Letters indicate significant differences between segments at 95% Confidence Level.
[66] 81 Fed. Reg. at 22613.
[67] InCrowd Survey 2023.
[68] Symphony NTRx_MATTY.
[69] We recognize the slight variability in the Limitations of Use across fenofibrate labeling. Our proposal seeks to achieve consistency across all fenofibrate labeling, though we would not object to inclusion of the dose equivalent should FDA prefer to do so.

> Fenofibrate did not reduce coronary heart disease morbidity and mortality in 2 large, randomized controlled trials of patients with type 2 diabetes mellitus. Multiple large, randomized controlled trials failed to establish an incremental benefit of fibrates, of which [DRUG (*i.e.*, the drug that is the subject of the labeling)] is a member, on cardiovascular morbidity and mortality over and above that demonstrated for statin monotherapy, including one trial in patients with TG levels between 200-499 mg/dL and HDL-C levels of 40 mg/dL or lower *[see Warnings and Precautions (5.1)]*.

Inclusion of this language would also be consistent with the Limitations of Use for Niaspan (niacin extended-release tablets). Similar to Trilipix, Niaspan was previously approved for use in combination with simvastatin or lovastatin, and, like Trilipix, its labeling included a Limitations of Use indicating that no incremental benefit of Niaspan add-on therapy had been established.[70] However, when FDA withdrew approval of Niaspan's statin co-administration indication, the Limitations of Use continued to refer to its lack of add-on benefit when added to a statin: "Addition of NIASPAN did not reduce cardiovascular morbidity or mortality among patients treated with simvastatin in a large, randomized controlled trial (AIM-HIGH)."[71]

- **Warnings and Precautions, Section 5**
    - *Section 5.1 Mortality and Coronary Heart Disease Morbidity* – Consistent with 21 C.F.R. § 201.57(c)(6)(i) and FDA's prior actions to incorporate the FIELD and ACCORD Studies' results into fenofibrate labeling, we request FDA similarly revise the labeling to include the PROMINENT Study results.

      First, we request that FDA include pemafibrate[72] in the list of drugs that are similar to fenofibrate and for which clinical trial results may also apply to fenofibrates. For example, Section 5.1, Mortality and Coronary Heart Disease Morbidity would be revised as follows: (with added text underlined):[73]

      > Because of similarities between fenofibrate, clofibrate, gemfibrozil, and pemafibrate, the findings in the following large randomized, placebo-controlled clinical studies with these fibrate drugs may also apply to [DRUG].

[70] *See* 81 Fed. Reg. at 22613.

[71] *See id*.; *see also* Niaspan (NDA 20381) USPI (Apr. 27, 2015).

[72] We recognize that FDA may prefer to instead refer to "non-U.S. approved pemafibrate" or "another fibrate" (or some other terminology when referencing pemafibrate). For clarity, we are not requesting that FDA adopt any particular terminology, and we use "pemafibrate" throughout only for convenience.

[73] Given variations across Section 5.1 of fenofibrate labeling, we recognize that slight adjustments of the text may be needed for each fenofibrate. *See, e.g.*, Triglide (NDA 21350) USPI § 5.1 (June 3, 2021).

Second, we request the following study information be added to Section 5.1 (added text underlined):

> The Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes (PROMINENT) trial was designed to address the residual question as to whether patients with high TG and low HDL cholesterol levels might derive substantial clinical benefit from decreased triglyceride levels, particularly in the type 2 diabetes population. In the randomized, placebo-controlled study of 10,497 subjects with type 2 diabetes, mild-to-moderate hypertriglyceridemia, low HDL-cholesterol, and well-controlled LDL-cholesterol (96% of subjects receiving statins), treatment with pemafibrate did not decrease the incidence of cardiovascular events, cardiovascular mortality, or all-cause mortality over a median follow-up of 3.4 years. The primary endpoint event occurred in 572 patients in the pemafibrate group and in 560 of those in the placebo group (hazard ratio, 1.03; 95% confidence interval, 0.91 to 1.15), with no apparent effect modification in any prespecified subgroup.

- *Section 5.3 Myopathy and Rhabdomyolysis* – The co-administration of fenofibrates with statins can increase risks associated with rhabdomyolysis. There is no dispute that these risks are "clinically significant adverse reactions" with, at minimum, "reasonable evidence of causal association," as required by 21 C.F.R. § 201.57(c)(6)(i).[74] Indeed, fenofibrate labeling already includes these risks, though with only limited information regarding statin interactions. Moreover, the risks associated with statin co-administration are particularly significant when contrasted with the absence of any clinical cardiovascular benefit. We recognize that no fenofibrate is currently approved for statin co-administration, but, as explained *supra*, Section B.1, this common prescribing practice has continued notwithstanding FDA's withdrawal of the statin co-administration indication. Therefore, these adverse reactions, which have clear implications for prescribing decisions and patient management, warrant labeling revisions.[75] For Section 5.3, we request FDA to revise the text as follows (with additions underlined):

  > Data from observational studies suggest that the risk for rhabdomyolysis is increased when fibrates are co-administered with a statin. Multiple well-controlled clinical trials did not

[74] *See also* Oct. 2013 AC Tr. at 291 ("[T]alking about safety, the data about fibrates and statin interactions … [is] very, very real. … And every EMR [electronic medical record] sets off alarms when you want to use a statin with a fibrate.").
[75] *See* W&P Guidance.

> demonstrate an incremental benefit of fibrates co-administered with a statin over statin monotherapy on cardiovascular morbidity and mortality in patients with Type 2 diabetes mellitus. [DRUG] is not FDA-approved for co-administration with statins, and the combination with a statin should be avoided unless further alterations in lipid levels is likely to outweigh the increased risk of this drug combination.

This revision would also help ensure consistent warning information across fenofibrate labeling, as certain fenofibrates already communicate that the combination with a statin should be avoided in the absence of a benefit that outweighs the risk.[76]

- *Section 5.10 Venothromboembolic Disease* – The co-administration of fenofibrates with statins can also increase risks associated with VTE. As with rhabdomyolysis, there is no dispute that these risks are "clinically significant adverse reactions" with, at minimum, "reasonable evidence of causal association," as required by 21 C.F.R. § 201.57(c)(6)(i).[77] Fenofibrate labeling already includes these risks, though with only limited information regarding statin interactions. Moreover, the risks associated with statin co-administration are particularly significant when contrasted with the absence of any clinical benefit.

  Again, we recognize that no fenofibrate is currently approved for statin co-administration, but, as explained *supra*, B.1, this common prescribing practice has continued notwithstanding FDA's withdrawal of the statin co-administration indication. Therefore, these adverse reactions, which have clear implications for prescribing decisions and patient management, warrant labeling revisions.[78] For Section 5.10, we request that FDA add the results of the PROMINENT Study to the labeling, which already references the FIELD Study and the Coronary Drug Project (adding the underlined text as follows):

  > In the PROMINENT trial, the number of patients with investigator-reported thromboembolism (VTE) was higher in the pemafibrate group that in the place group (in 71 patients versus 35 patents; hazard ratio, 2.05; 95% CI, 1.35 to 3.17; $p < 0.001$).

[76] *See, e.g.*, Tricor (NDA 21656) USPI § 5.3 (June 3, 2021).

[77] *See also* Oct. 2013 AC Tr. at 291 ("[T]alking about safety, the data about fibrates and statin interactions … [is] very, very real. … And every EMR [electronic medical record] sets off alarms when you want to use a statin with a fibrate.").

[78] *See* W&P Guidance. As explained above, *supra*, Section B.1, the increased risk of VTE observed in the PROMINENT Study is consistent with recent observational data regarding the association of fenofibrates with increased VTE risk.

4. *Dear Health Care Provider (DHCP) Letter and Drug Safety Communications*

DHCP letters are intended to "alert physicians and other health care providers about important new or updated information regarding a human drug," including information that "could affect the decision to use a drug or require some change in behavior by health care providers, patients, or caregivers."[79] The PROMINENT Study and the labeling changes warranted by the trial's results categorically constitute such information. Indeed, the above-described labeling changes convey a limitation of the indication as well as provide clinically important new information about known adverse reactions and identify subpopulations (*i.e.*, those on statins) for whom the drug should be used with added caution. As FDA has recognized, this is precisely the type of information that should be communicated in DHCP letters.[80] Accordingly, we request that FDA require the holders of approved marketing applications for fenofibrate products to issue DHCP letters immediately upon completion of the labeling changes.

Additionally, we request that FDA issue a DSC to communicate the results of the PROMINENT Study, with a subsequent update once the labeling changes have been implemented. This vehicle, consistent with FDA's approach for the ACCORD Lipid Study results,[81] will enable timely and effective conveyance of information critical to professionals and patients as they make informed treatment decisions. Given the continued misperceptions about the ability of fenofibrates, alone, or in combination with statins to address residual cardiovascular risk, expedient dissemination of the PROMINENT trial—and its debunking of the persistent belief that fenofibrate add-on therapy can benefit certain populations—is imperative to ensure that patients are receiving the care they need and the safe and effective treatments necessary to manage their conditions.

HealthyWomen provides trusted, evidence-based, unbiased and timely health information for women. HealthyWomen can help amplify and further distribute the DSC letter to its community to support timely and informed decisions about their health. *Conclusion*

The evidence is clear—as recently demonstrated in the PROMINENT Study, fibrate add-on therapy does not yield any incremental cardiovascular benefit over statins, though it does pose risks. To help address the cardiovascular disease crisis facing Americans and to help ensure that women are not prescribed unnecessary drugs that may lead them to forego drugs that work

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[79] *See* FDA Guidance for Industry, *Dear Health Care Provider Letters: Improving Communication of Safety Information* (Jan. 2014) ("DHCP Guidance"); *see also* 21 C.F.R. § 200.5.

[80] *See* DHCP Guidance.

[81] *See* FDA, Statement to Healthcare Professionals on the ACCORD Lipid Trial from the FDA's Center for Drug Evaluation and Research (Mar. 15, 2010) (explaining that FDA planned to review the ACCORD trial "to determine how the study's findings relate to the approved indication and labeling for Trilipix" and urging healthcare professionals to "consider the available clinical information on simvastatin and fenofibrate when decisioning what cholesterol-lowering medications to prescribe"); *see also* FDA Drug Safety Communication: Review update of Trilipix (fenofibric acid) and the ACCORD Lipid trial (Nov. 9, 2011) (informing the public that Trilipix "may not lower a patient's risk of having a heart attack or stroke" based on the data from the ACCORD trial and highlighting changes to Trilipix's labeling).

petitioners urge FDA to take the requested actions to effectively communicate this critical information implicating the fenofibrate benefit-risk profile. Without further FDA action, patients will continue to be undertreated and women underserved for residual cardiovascular risk, and exposed to unnecessary risks presented by fenofibrates, and payors will continue to incur unnecessary costs.

C. Environmental Impact

The actions requested in this Petition are subject to categorical exclusion under 21 C.F.R. § 25.31(b), as the action will not increase the use of the active moiety.

D. Economic Impact

Pursuant to 21 C.F.R. § 10.30(b), an economic impact statement will be submitted upon request of the Commissioner.

E. Certification

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

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