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February 25, 2014

Margaret A. Hamburg, M.D.
Commissioner
Food and Drug Administration
Department of Health and Human Services
WO 2200
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Dear Dr. Hamburg:

Public Citizen, a consumer advocacy organization with more than 300,000 members and supporters nationwide, hereby petitions the Food and Drug Administration (FDA), pursuant to the Federal Food, Drug and Cosmetic Act 21 U.S.C. § 352 and 21 C.F.R. §§ 10.30 and 201.56, to immediately take the following actions with respect to testosterone-containing drugs currently on the market in the U.S.

Actions Requested

We hereby petition the FDA to add a black box warning about the increased risks of heart attacks and other cardiovascular dangers to the product labels of all testosterone-containing drugs presently on the market in the U.S.¹

We urge the FDA to ask manufacturers to send “Dear Doctor” letters to warn physicians of these serious adverse effects and to require that the FDA-approved Medication Guide for testosterone products, dispensed to patients when their prescriptions are filled, be updated to include this new warning.

¹ Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. <http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm>. Accessed February 19, 2014. Search by active ingredient, then type in “testosterone.”

Finally, we urge the FDA to delay its decision date on approving a new long-acting injectable testosterone product Avedd (testosterone undecanoate, Endo), now set for February 28, 2014, because its approval, absent the new black box warning, would cause further cardiovascular harm to patients for whom this new formulation is prescribed.

Statement of Grounds

The urgency for this action is highlighted by the massive prescribing of testosterone-containing products, with more than 400,000 prescriptions filled in the U.S. in December 2013 alone and more than 5 million filled during all of 2013.²

Despite increasing evidence of significant cardiovascular risk from an analysis of 27 randomized clinical trials and, most recently, from a large observational study involving 45 times more testosterone-exposed men than the largest previous study,^{3,4} warnings of testosterone-induced cardiovascular risk are dangerously absent from the current FDA-approved labeling for all of these products.

In the face of this accumulating evidence, the FDA was reckless, from a public health perspective, to state three weeks ago that it “has not concluded that FDA-approved testosterone treatment increases the risk of stroke, heart attack, or death.”⁵ As part of this announcement, the agency further stated, “The first publication that prompted FDA to reassess the cardiovascular safety of testosterone therapy was an observational study of older men in the U.S. Veteran Affairs (VA) health system published in the *Journal of the American Medical Association (JAMA)* in November 2013.”⁶ This *JAMA* study had been preceded in 2010 by a randomized, placebo-controlled trial that was stopped before completion because of a significant excess of cardiovascular events in older men randomized to get testosterone instead of a placebo.⁷

Furthermore, an April 2013 meta-analysis of 27 previous randomized trials comparing testosterone to a placebo in men found a statistically significant increase in cardiovascular events

² IMS Data on U.S. testosterone prescriptions for gel, patch and oral dosage forms, 2013.

³ Finkle, WD, Greenland S, Ridgeway GK, et al. Increased risks of non-fatal myocardial infarction following testosterone therapy prescription in men. *PLoS ONE* 9(1): e85805. doi:10.1371/journal.pone.0085805 <http://www.ncbi.nlm.nih.gov/pubmed/24489673>. Accessed February 21, 2014.

⁴ Vigen R, O'Donnell CI, Barón AE, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *JAMA* 2013;310: 1829-1836.

⁵ Food and Drug Administration. FDA evaluating risk of stroke, heart attack and death with FDA-approved testosterone products. January 31, 2014. <http://www.fda.gov/Drugs/DrugSafety/ucm383904.htm>. Accessed February 20, 2014.

⁶ Vigen R, O'Donnell CI, Barón AE, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *JAMA* 2013;310: 1829-1836.

⁷ Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with testosterone administration. *N Engl J Med.* 2010;363(2):109-22.

and cardiovascular deaths in men getting testosterone in comparison to those receiving placebo.⁸ We must question why none of these earlier studies “prompted FDA to reassess the cardiovascular safety of testosterone.”

Summary of Randomized, Placebo-Controlled Clinical Trials: Evidence of Increased Cardiovascular Risk with Testosterone

Basaria, et al, July 2010:⁹ This randomized, placebo-controlled trial involved 209 men who had limitations in mobility and low testosterone levels. Subjects were randomly assigned to receive testosterone gel or placebo gel, to be applied daily for six months. The study was stopped before completion because of a significant five-fold increase in cardiovascular events, including heart attacks and a stroke, in men getting testosterone compared to those getting a placebo. Because of the relatively small number of events, the authors were cautious about the conclusions of the study but importantly, the data and safety monitoring board recommended that the study be stopped because of the higher rate of adverse cardiovascular events in the testosterone group.

Xu, et al, April 2013:¹⁰ This was a landmark meta-analysis of 27 previous, smaller randomized trials, including the Basaria study above, all of which compared testosterone with placebo. The meta-analysis involved a total of 2,994 men and therefore had considerably more cardiovascular events — a total of 180 — than in the smaller trials, which (except for Basaria) did not individually find a statistically significant increase in cardiovascular events.

One of the most remarkable findings of the meta-analysis was that the 13 drug industry-funded trials collectively failed to show any increase in cardiovascular events in the testosterone subjects, but the 14 non-industry-funded trials collectively showed a significant 2.06-fold increased risk with testosterone. There was a significant difference between the cardiovascular risk results from the industry-funded studies and the clearly positive results from those studies not industry-funded. But even with the inclusion of the 13 industry-funded studies, the overall findings of the meta-analysis were that testosterone increased the risk of a cardiovascular-related event, the odds ratio for increased risk being 1.54, (95% confidence interval (CI) 1.09 to 2.18). In addition, 33 cardiovascular-related deaths were identified (22 testosterone arm and 11 placebo arm), for which the odds ratio, at 1.42 (95% CI 0.70 to 2.89), was similar to the estimate for all cardiovascular-related events. The authors’ conclusion, stated in the abstract, forms one of the bases for this petition for a black box warning: “The effects of testosterone on cardiovascular-

⁸ Xu L, Freeman G, Cowling BJ, Schooling CM. Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled trials. *BMC Medicine* 2013;11:108.

⁹ Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with testosterone administration. *N Engl J Med.* 2010;363(2):109-22.

¹⁰ Xu L, Freeman G, Cowling BJ, Schooling CM. Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled trials. *BMC Medicine* 2013;11:108.

related events varied with source of funding. Nevertheless, overall and particularly in trials not funded by the pharmaceutical industry, exogenous testosterone increased the risk of cardiovascular-related events, with corresponding implications for the use of testosterone therapy.” The authors added that “Our findings are consistent with the three previous meta-analyses,^{11,12,13} which all indicated a non-significantly higher risk of testosterone therapy for a composite cardiovascular outcome of the events.”

Summary of Observational Studies: Evidence for Increased Cardiovascular Risk with Testosterone

Vigen et al, November 2013:¹⁴ The study the FDA referred to as “the first publication that prompted FDA to reassess the cardiovascular safety of testosterone” involved men with low testosterone levels who underwent coronary angiography in the VA system between 2005 and 2011. Of the 8,709 men with low testosterone levels, 1,223 started testosterone therapy after a median of 531 days following coronary angiography. Adjusting for the presence of coronary artery disease, testosterone therapy was associated with increased risk of adverse outcomes (hazard ratio, 1.29; 95% CI, 1.04 to 1.58) compared to the risk in those 7,468 men who did not get testosterone therapy. The authors concluded: “Among a cohort of men in the VA health care system who underwent coronary angiography and had a low serum testosterone level, the use of testosterone therapy was associated with increased risk of adverse outcomes. These findings may inform the discussion about the potential risks of testosterone therapy.”¹⁵ This study was not industry-funded.

Finkle et al, January 2014:¹⁶ This NIH-funded study included 45 times as many men using testosterone (55,593) than any previous single study. The study was prompted, in part, by the

¹¹ Calof OM, Singh AB, Lee ML, et al. Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo-controlled trials. *J Gerontol A Biol Sci Med Sci.* 2005; 60(11):1451–1457.

¹² Haddad RM, Kennedy CC, Caples SM, et al. Testosterone and cardiovascular risk in men: a systematic review and meta-analysis of randomized placebo-controlled trials. *Mayo Clin Proc.* 2007;82(1):29–39.

¹³ Fernandez-Balsells MM, Murad MH, Lane M, et al. Clinical review 1: adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis. *J Clin Endocrinol Metab.* 2010; 95(6):2560–2575.

¹⁴ Vigen R, O’Donnell CI, Barón AE, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *JAMA* 2013 310: 1829-1836.

¹⁵ Vigen et al noted an earlier VA system retrospective observational study comparing 398 men treated with testosterone and 633 patients not treated with testosterone (Shores MM, Smith NL, Forsberg CW, et al. Testosterone treatment and mortality in men with low testosterone levels. *J Clin Endocrinol Metab.* 2012;97(6):2050-2058). This earlier study revealed a 39 percent reduction in the risk of death in testosterone-treated men. However, Vigen et al noted that “[t]hese discrepant results may be due to differences in the patient populations and methods used to control for confounding.”

¹⁶ Finkle, WD, Greenland S, Ridgeway GK, et al. Increased risks of non-fatal myocardial infarction following testosterone therapy prescription in men. *PLoS ONE* 9(1): e85805. doi:10.1371/journal.pone.0085805 <http://www.ncbi.nlm.nih.gov/pubmed/24489673>. Accessed February 21, 2014.

findings of the 2010 Basaria study, discussed above. The authors were thus able, for the first time, to examine: (1) the risk of heart attacks alone rather than increases in overall cardiovascular events, (2) the risk in younger men (since previous studies had focused mainly on older men), and (3) the risk within the first 90 days following initiation of testosterone use compared with the heart attack risk in the year preceding testosterone treatment in the same men.

The statistically significant findings were that the risk of heart attacks after using the drug for three months was twice the risk in the year before use in all men 65 and over. Furthermore, the study found for the first time that in those men under 65 with a history of heart disease, there was a 2.9-fold increase in heart attack risk.

Conclusions

Thus, the rapidly accumulating evidence from both randomized, placebo controlled trials and from observational studies, such as the one discussed above involving 55,000 men, make it clear that testosterone treatment increases the risks of cardiovascular diseases, including heart attacks. For the FDA to continue to further delay action because, as it said in its January 31 announcement,¹⁷ it “has not concluded that FDA-approved testosterone treatment increases the risk of stroke, heart attack, or death,” is a betrayal of its role in the U.S. Public Health Service.

The FDA announcement¹⁸ did make clear that “testosterone products are FDA-approved *only* for use in men who lack or have low testosterone levels in conjunction with an associated medical condition. Examples of these conditions include failure of the testicles to produce testosterone because of reasons such as genetic problems or chemotherapy.... None of the FDA-approved testosterone products are approved for use in men with low testosterone levels who lack an associated medical condition.”

But the hyped-up nature of the “low-T” advertising campaigns ensures that many U.S. men who do not meet the FDA-specified criteria of both low testosterone levels *and* an associated medical condition due to hypogonadism are taking the products nonetheless. Evidence of the success of these campaigns can be seen in the recent finding that almost 25% of men prescribed testosterone in this country had not previously even had a blood test to determine if their testosterone level was low.¹⁹

¹⁷ Food and Drug Administration. FDA evaluating risk of stroke, heart attack and death with FDA-approved testosterone products. January 31, 2014. <http://www.fda.gov/Drugs/DrugSafety/ucm383904.htm>. Accessed February 20, 2014.

¹⁸ *Ibid.*

¹⁹ Baillargeon J, Urban RJ, Ottenbacher KJ, Pierson KS, Goodwin JS. Trends in androgen prescribing in the United States, 2001 to 2011. *JAMA Intern Med* 2013;173:1465-6.

Unless the FDA immediately begins to provide adequately strong black box warnings about the risks of heart attacks and other cardiovascular diseases, the continuing toll of heart attacks in people who are not even candidates for testosterone will continue. At the present rate of prescribing, approximately 13,000 prescriptions for testosterone products are filled each day in this country.²⁰ Each day of delay of the boxed warning ensures much more exposure, too often for men who cannot benefit from the drug but will only be exposed to its risks.

Summary of Petition Requests

For the reasons stated above, pursuant to the Federal Food, Drug and Cosmetic Act 21 U.S.C. § 352, and 21 C.F.R. §§ 10.30 and 201.56, we hereby petition the FDA to:

- (1) immediately add a black box warning about the increased risks of heart attacks and other cardiovascular dangers to the product labels of all testosterone-containing drugs presently on the market in the United States;
- (2) ask manufacturers to send “Dear Doctor” letters to warn physicians of these serious adverse effects;
- (3) require that the FDA-approved Medication Guide for testosterone products, dispensed to patients when their prescriptions are filled, be updated to include this new warning; and
- (4) delay the agency’s decision date on approving a new long-acting injectable testosterone product Aveed (testosterone undecanoate, Endo), now set for February 28, because its approval, absent the new black box warning, would cause further cardiovascular damage to new users.

Environmental Impact Statement

Nothing requested in this petition will have an impact on the environment.

²⁰ IMS Data on U.S. testosterone prescriptions for gel, patch and oral dosage forms, 2013.

Certification

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: January 15, 2014. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: None. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Sincerely,



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



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