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RE: Citizen Petition – Docket Number FDA-2011-P-0785

Dear Dr. Hamburg and Dr. Woodcock:

Public Citizen, a consumer group representing more than 250,000 members and supporters nationwide, wishes to supplement its October 26, 2011 petition to the Food and Drug Administration (FDA) (docket number FDA-2011-P-0785).[1]

I. SUMMARY AND STATUS OF ORIGINAL PETITION

In our petition, we requested that the 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, immediately require the following:

(1) The addition of a black box warning to the label for tigecycline (Tygacil, Pfizer Pharmaceuticals, Inc.; there is currently no black box warning on the drug label) indicating that the antibiotic:

(a) has an increased risk of death in comparison to many other antibiotics when used to treat a variety of serious infections; and

(b) should be used only as a last-resort antibiotic in the treatment of serious infections, and then only in combination with one or more bactericidal antibiotics.

(2) The distribution of an FDA-approved patient Medication Guide containing a warning about the above-mentioned increased risk of death and the need for restricted use, to be dispensed to the patient prior to the administration of the first dose of a course of tigecycline.

(3) The distribution by Pfizer of a Dear Doctor letter alerting physicians to this adverse effect warning and the need for restricted use of the drug.

In our petition, we noted that serious safety signals suggesting a higher mortality rate with tigecycline than with comparator antibiotics were readily apparent from the pivotal clinical trials prior to its approval in 2005 and presented in the initial New Drug Application (NDA), #21-821, for tigecycline. Furthermore, we cited the FDA's pooled analysis of the randomized clinical trials comparing tigecycline to other approved antibiotics for a variety of serious infections,[2] as well as a recently published systematic review and meta-analysis,[3] demonstrated that, across all trials, the overall risk of death in those subjects treated with tigecycline was approximately 20 to 30% higher than in subjects treated with comparator antibiotics. We concluded that given the seriousness of these findings, the FDA's July 2010 update of the "Warnings and Precautions" and "Adverse Reactions" sections of the label for tigecycline is insufficient in terms of both content and prominence within the label.

We have not yet received a decision from the agency on our petition.

II. SUPPLEMENTAL INFORMATION

Since the submission of our original petition, Prasad et al have published on-line another meta-analysis of the randomized clinical trials comparing tigecycline to other approved antibiotics for a variety of serious infections (copy of enclosed),[4] which reaffirms the results of the FDA's pooled analysis of these trials and those of another recently published systematic review and meta-analysis by Yahav et al cited in our original petition.[5,6]

As with the prior analyses described in our original petition, Prasad et al found that across 10 published and three unpublished randomized controlled trials, tigecycline was associated with increased mortality, with an absolute risk difference (RD) of 0.7% (95%

confidence interval [CI], 0.1%-1.2%, P=0.01). They also reported that tigecycline was associated with increased non-cure rates (RD, 2.9%; 95% CI, 0.6%-5.2%; P=0.01).

Prasad et al also reported that a pooled analysis of the five trials already completed by early 2005, ***before*** tigecycline was approved by FDA, would have demonstrated a similar harmful effect of tigecycline on survival (RD for mortality 0.7%, P=0.06), which is very similar to the overall results of their meta-analysis of all 13 studies and to the results of the meta-analyses published by the FDA in 2010 and by Yahav et al in 2011. In discussing these observations, Prasad et al noted the following:[7]

> The FDA was aware of consistent increases in mortality and infectious complications across tigecycline studies in 2005, but was concerned about the hazards of aggregating data from different types of infection. Even given this decision, convening a public Anti-Infective Advisory Committee meeting in 2005 and closely reexamining mortality annually by meta-analysis might have provided additional opportunities to recognize the association of tigecycline with excess deaths.

They concluded the following:[8]

> Clearly, tigecycline should not be used when other effective antibiotic choices are available. Using tigecycline in life-threatening infections for which there are few or no alternative agents may be justifiable, but is only supported by anecdotal evidence.

In an accompanying editorial (copy enclosed), Powers provided the following comments on the study by Prasad et al:[9]

> In this issue of *Clinical Infectious Diseases*, Prasad and colleagues present a meta-analysis of 13 randomized trials comparing outcomes with tigecycline to control antimicrobials. Their results show an absolute mortality increase of 0.7% (95% CI 0.1% to 1.2%) with tigecycline, translating into one excess death for every 143 patients treated (95% CI 83 to 1000). The estimates of increased mortality were consistent across diseases, with greater mortality in the more serious and life-threatening diseases. An evaluation of "non-cure" showed evidence of greater lack of effectiveness with tigecycline, with an absolute difference of 2.9% (95% CI 0.6% to 5.2%). This translates into one person experiencing "noncure" for every 34 patients treated (95% CI 19 to 166). While this data hints at lack of effectiveness as the cause for increased mortality, it is not possible to rule out unknown toxicity of tigecycline contributing to both lack of effectiveness and increased mortality.
>
> The authors' conclusions are similar to [the FDA's] evaluation in a public health warning. The authors' methods are thorough and include more information than previously published meta-analyses. Since these trials are randomized, **one can**

> **causally ascribe the increased mortality to tigecycline and not to other confounding factors** [emphasis added].
>
> These results have implications for both clinical practice and for the methodology of antimicrobial studies, evaluations by regulatory agencies and marketing by pharmaceutical companies. **The results have clinical significance as any increase in mortality is clinically important. The numbers needed to harm show a substantial number of patients could be harmed especially in common, serious diseases where lack of effectiveness can result in death** [emphasis added].

The data presented by Prasad et al and the commentary provided by Powers in his accompanying editorial provide further support for the actions requested in our original petition to the FDA. We urge the FDA to act expeditiously and grant our petition.

III. ENVIRONMENTAL IMPACT STATEMENT

Nothing requested in this supplement to our original petition will have an impact on the environment.

IV. CERTIFICATION

We certify that, to the best of our knowledge and belief, our original petition and this supplement include all information and views on which this petition relies, as well as representative data and information known to the petitioners which are unfavorable to the petition.

Sincerely,

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Public Citizen's Health Research Group

Sidney M. Wolfe, M.D.
Director
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Enclosures

[1] Carome MA, Wolfe SM. Petition to the FDA to add a black box warning to the label for tigecycline (Tygacil, Pfizer Pharmaceuticals, Inc.). October 26, 2011. Available at http://www.citizen.org/hrg1977. Accessed May 14, 2012.
[2] The Food and Drug Administration. FDA drug safety communication: increased risk of death with Tygacil (tigecycline) compared to other antibiotics used to treat similar infections. September 1, 2010. Available at http://www.fda.gov/Drugs/DrugSafety/ucm224370.htm. Accessed May 14, 2012.
[3] Yahav D, Lador A, Paul M, Leibovici L. Efficacy and safety of tigecycline: a systematic review and meta-analysis. J Antimicrob Chemother. 2011;66:1963-1971.
[4] Prasad P, Sun J, Danner R, Natanson C. Excess deaths associated with tigecycline after approval based on noninferiority trials. Clin Infect Dis. Published online March 30, 2012. doi:10.1093/cid/cis270.
[5] The Food and Drug Administration. FDA drug safety communication: increased risk of death with Tygacil (tigecycline) compared to other antibiotics used to treat similar infections. September 1, 2010. Available at http://www.fda.gov/Drugs/DrugSafety/ucm224370.htm. Accessed may 14, 2012.
[6] Yahav D, Lador A, Paul M, Leibovici L. Efficacy and safety of tigecycline: a systematic review and meta-analysis. J Antimicrob Chemother. 2011;66:1963-1971.
[7] Prasad P, Sun J, Danner R, Natanson C. Excess deaths associated with tigecycline after approval based on noninferiority trials. Clin Infect Dis. Published online March 30, 2012. doi:10.1093/cid/cis270.
[8] Prasad P, Sun J, Danner R, Natanson C. Excess deaths associated with tigecycline after approval based on noninferiority trials. Clin Infect Dis. Published online March 30, 2012. doi:10.1093/cid/cis270.
[9] Powers JH. Asking the right questions: morbidity, mortality and measuring what's important in an unbiased evaluation of antimicrobials. Clin Infect Dis. Published online March 30, 2012 doi:10.1093/cid/cis274.