DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
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Silver Spring, MD 20993

AUG 0 4 2014

Sidney M. Wolfe, M.D.
Michael A. Carome, M.D.
Public Citizen
1600 20th Street, NW
Washington, DC 20009

Re: Docket No. FDA-2011-P-0785

Dear Dr. Wolfe and Dr. Carome:

This responds to your citizen petition (Petition) received on October 28, 2011. In the Petition, you request that the Food and Drug Administration (FDA or the Agency) immediately require the following:

1) The addition of a "black box" warning to the label for Tygacil (tigecycline) 50 Milligrams/Vial (mg/vial) 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 increased risk of death and the need for restricted use, to be dispensed prior to the administration of the first dose of a course of Tygacil.
3) The distribution by Pfizer of a Dear Doctor letter alerting physicians to your proposed adverse effect warning and the need for restricted use of Tygacil.

We have carefully considered the Petition and a supplement to it dated May 15, 2012 (Petition Supplement). For the reasons described in detail below, the Petition is granted in part and denied in part.

We agree that information about increased mortality associated with the use of Tygacil should be presented as a boxed warning on the Tygacil labeling. On September 26, 2013, we approved revisions to the Tygacil labeling to include a boxed warning about the increased risk of mortality. Your request that Tygacil should be used only as a last-resort antibacterial drug has also been addressed by the labeling changes approved on September 26, 2013. The boxed warning, which has been added to the product's labeling, includes the statement, "Tygacil should be reserved for use in situations when alternative treatments are not suitable." We deny your request to include a statement in the boxed warning that Tygacil should be used "only in combination with one or more bactericidal antibiotics." We also deny your request that FDA require an FDA-approved

patient Medication Guide and your request that FDA require Pfizer to distribute a Dear Doctor letter.

I. BACKGROUND

A. Tygacil (tigecycline)

Tygacil (tigecycline) is a tetracycline-class antibacterial drug and is generally considered bacteriostatic, i.e. the drug inhibits bacterial growth but does not necessarily kill the bacteria. The antibacterial spectrum of tigecycline (i.e., the bacteria against which tigecycline is active) includes Gram-positive and Gram-negative organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA), *Legionella pneumophila,* and some *Mycobacteria*. Tigecycline is not active against *Pseudomonas aeruginosa* and has decreased activity against *Proteus*, *Providencia*, and *Morganella* species.

Each Tygacil vial contains 50 mg tigecycline lyophilized powder for intravenous infusion. FDA approved Tygacil (tigecycline) for Injection, 50 mg/vial for the treatment of complicated skin and skin structure infections (cSSSI) and complicated intra-abdominal infections (cIAI) on June 15, 2005, (new drug application (NDA) 021821) in patients 18 years of age and older. On March 20, 2009, FDA approved a third indication for Tygacil, community-acquired bacterial pneumonia (CABP) in patients 18 years of age and older. Tigecycline has failed to demonstrate non-inferiority to comparator antibacterial drugs in trials for the treatment of hospital-acquired pneumonia (HAP) including ventilator-associated pneumonia (VAP) and diabetic foot infections (DFI) and is not approved for these indications.

B. Warnings in Prescription Drug Labeling

FDA regulations state that the WARNINGS AND PRECAUTIONS section of a prescription drug's full prescribing information must describe clinically significant adverse reactions, other potential safety hazards, limitations in use imposed by them, and steps that should be taken if these situations occur.[1] Labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association of the hazard with a drug.[2] For products described in § 201.56(b)(1) (21 CFR 201.56(b)(1)), a summary of the most clinically significant warnings and precautions information must be included in the HIGHLIGHTS OF PRESCRIBING INFORMATION (HIGHLIGHTS) section of the labeling.[3]

Under § 201.57(c)(1), a boxed warning (sometimes referred to as a "black box" warning) may be required for certain contraindications or serious warnings, particularly those that may lead to death or serious injury.[4] A boxed warning must contain, in uppercase letters, a heading that includes the word "WARNING" and conveys the general focus of information in the box. A boxed warning briefly explains the risk and refers to more detailed information in the

[1] 21 CFR 201.57(c)(6)(i); see also 21 CFR 201.80(e) and (f).
[2] 21 CFR 201.57(c)(6)(i).
[3] 21 CFR 201.57(a)(10).
[4] See also 21 CFR 201.80(e).

CONTRAINDICATIONS or WARNINGS AND PRECAUTIONS section.[5] A summary of a boxed warning (with the heading WARNING and other words identifying the subject of the warning) must be included in the HIGHLIGHTS in a box and in bold type.[6]

FDA's guidance for industry *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products—Content and Format* (Warnings Guidance)[7] states on page 11 that a boxed warning ordinarily is used to highlight one of the following situations:

- There is an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using the drug OR

- There is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation) OR

- FDA approved the drug with restrictions to ensure safe use because FDA concluded that the drug can be safely used only if its distribution or use is restricted (e.g., under 21 CFR 314.520 and 601.42 "Approval with restrictions to assure safe use" or under 505-1(f)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) "Risk Evaluation and Mitigation Strategies" elements to assure safe use).

The Warnings Guidance also states that there may be other situations in which a boxed warning may be appropriate to highlight information that is especially important to a prescriber.[8]

C. Medication Guides

Part 208 of the Code of Federal Regulations (21 CFR 208.1-208.26) sets forth requirements for Medication Guides for human prescription drug products, including biological products, that the Agency determines pose a serious and significant public health concern requiring distribution of FDA-approved patient information. The purpose of Medication Guides, as specified by regulation, "is to provide information when the FDA determines in writing that it is necessary to patients' safe and effective use of drug products" (21 CFR 208.1(b)).

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[5] 21 CFR 201.57(c)(1).
[6] 21 CFR 201.56(d)(1) and 201.57(a)(4).
[7] FDA guidance for industry *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format*, October 2011, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075096.pdf.
[8] Id. at 11-12.

As noted in 21 CFR 208.1(c), "[p]atient labeling will be required if the FDA determines that one or more of the following circumstances exists:

(1) The drug product is one for which patient labeling could help prevent serious adverse effects.
(2) The drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decision to use, or to continue to use, the product.
(3) The drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness."

II. DISCUSSION

You request that FDA immediately require (1) the addition of a "black box" warning to the labeling for Tygacil 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 prior to the administration of the first dose of a course of tigecycline; and (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 the Petition, you support your requests by stating that past safety signals, FDA's pooled analysis, and recently published meta-analyses suggest a higher mortality rate with tigecycline than with comparator antibiotics (Petition at 2, Petition Supplement at 2).

We discuss each of your requests in further detail below.

A. Request to Add a Boxed Warning

You request that FDA require the addition of a boxed warning to the label for Tygacil indicating that the antibiotic has an increased risk of death in comparison to many other antibiotics when used to treat a variety of serious infections (Petition at 1). You also request that FDA require that the boxed warning include language indicating that Tygacil 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 (Petition at 1). You state that the Tygacil label at the time your Petition was submitted was insufficient in light of the information you provided (Petition at 9). You also state that the label updates made in July 2010 to the WARNING AND PRECAUTIONS section to include information on all-cause mortality, mortality imbalance, and lower cure rates in VAP were inadequate in terms of both content and prominence on the label (Petition at 9).

We grant your request to add a boxed warning to the Tygacil labeling indicating that Tygacil has an increased risk of death compared with comparator antibacterial drugs. A boxed warning with this information has been added to the WARNINGS AND PRECAUTIONS section of the Tygacil labeling along with information regarding a recent FDA meta-analysis that demonstrated

an increase in all-cause mortality in Tygacil-treated patients compared to controls. The boxed warning that has been added to the labeling also includes the statement, "Tygacil should be reserved for use in situations when alternative treatments are not suitable."

We have concluded that your proposed language regarding the use of Tygacil only in combination with one or more bactericidal antibiotics (Petition at 1) will not convey accurate information to health care providers and should not be included in labeling. Tygacil has not been evaluated in combination with other antibacterial drugs in clinical trials reviewed by FDA. Such a recommendation in product labeling may lead to unnecessary antibacterial drug exposure, higher adverse event and resistance rates, and potential adverse drug interactions.

We discuss below background regarding the Tygacil labeling and clinical studies, FDA's response to the data you provided in support of your requests, and its rationale for approving the recent labeling changes.

1. Pivotal Clinical Trials Presented in the Initial Application for Tygacil NDA 021821 and Original Approved Labeling

In the Petition, you state that serious safety signals suggesting a higher mortality rate with tigecycline than with comparator antibacterial drugs were readily apparent from the pivotal clinical trials presented in the initial application for NDA 021821 (Petition at 2). You state that all four pivotal studies from the initial NDA 021821 showed higher mortality rates in subjects receiving tigecycline in comparison to subjects receiving the comparator antibiotics (Petition at 3). You also conclude that compared to other antibacterial drugs, tigecycline-treated subjects with complicated intra-abdominal infections showed increased rates of several infection-related adverse events, including pneumonia, sepsis, peritonitis, abscess, and hypotension (Petition at 4). Lastly, you state that the rates of nausea and vomiting were markedly higher in tigecycline-treated subjects compared with subjects treated with comparator antibacterial drugs (Petition at 4).

The approval of Tygacil was based on the analysis of four randomized, double-blind clinical trials that included Tygacil and comparator drugs. Two of these studies were for the treatment of cSSSI and two for cIAI. FDA's review of these trials concluded Tygacil met the standard for approval for use in the treatment of cSSSI and cIAI.

Two phase 3 trials, studies 301 and 306, compared tigecycline to imipenem/cilastatin in cIAI.[9] Diagnoses included appendicitis, cholecystitis, diverticulitis, gastric/duodenal perforation, intra-abdominal abscess, perforation of intestine, and peritonitis. The trials were designed to compare clinical outcome at the test-of-cure visit in the microbiologic modified intent-to-treat (m-mITT) and microbiologically evaluable (ME) populations. The two trials demonstrated non-inferiority of tigecycline to the approved comparator based on a lower limit of the 2-sided 95% confidence interval (CI) for the difference in clinical cure rates greater than or equal to -15% (see Table 1).

[9] NDA 021821 Medical Review, June 2005, available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2005/021821Orig1s000MedR.pdf.

Table 1: Clinical outcome of cure in Tigecycline cIAI trials

Studies	Population	Tigecycline [a] n/N (%)	Imipenem/Cilastatin [b] n/N (%)	95% CI [c]
301	ME	199/247 (80.6)	210/255 (82.4)	(-9.0, 5.4)
	m-mITT	227/309 (73.5)	244/312 (78.2)	(-11.8, 2.3)
306	ME	242/265 (91.3)	232/258 (89.9)	(-4.0, 6.8)
	m-mITT	279/322 (86.6)	270/319 (84.6)	(-3.7, 7.7)

[a] 100 mg initially, followed by 50 mg every 12 hours
[b] Imipenem/Cilastatin (500 mg every 6 hours)
[c] 95% confidence intervals for the difference in clinical cure rates

Two phase 3 trials, studies 300 and 305, compared tigecycline to the combination of vancomycin and aztreonam in cSSSI.[10] The main diagnoses were deep soft tissue infections or major abscesses. The trials were designed to compare clinical outcome at the test-of-cure (TOC) visit in the clinical modified intent-to-treat (c-mITT) and clinically evaluable (CE) populations. The trials demonstrated non-inferiority of tigecycline to the comparators based on a lower limit of the 2-sided 95% CI for the difference in clinical cure rates greater than or equal to -15% (see Table 2).

Table 2: Clinical outcome of cure in Tigecycline cSSSI trials

Studies	Population	Tigecycline [a] n/N (%)	Vancomycin/Aztreonam [b] n/N (%)	95% CI [c]
300	CE	165/199 (82.9)	163/198 (82.3)	(-7.4, 8.6)
	c-mITT	209/277 (75.5)	200/260 (76.9)	(-9.0, 6.1)
305	CE	200/223 (89.7)	201/213 (94.4)	(-10.2, 0.8)
	c-mITT	220/261 (84.3)	225/259 (86.9)	(-9.0, 3.8)

[a] 100 mg initially, followed by 50 mg every 12 hours
[b] Vancomycin (1 gram (g) administered intravenously (IV) every 12 hours)/Aztreonam (2 g IV every 12 hours)
[c] 95% confidence intervals for the difference in clinical cure rates

There were more deaths in the tigecycline arms [32/1383 (2.3%)] than in comparator arms [22/1375 (1.6%)] in the four initial tigecycline trials, but the difference was not statistically significant. At the time of the initial NDA review, an analysis of the deaths observed in the trials was conducted to identify specific drug-related factors (whether safety issues or lack of efficacy) that might have contributed to this difference. The review concluded that no specific safety or efficacy findings could be found to account for this difference in mortality. Tygacil was approved for the treatment of cSSSI and cIAI in June 2005, and the labeling described the observed difference in mortality.

Additional information on the safety and efficacy of tigecycline was obtained in two clinical trials of tigecycline for the treatment of CABP that were subsequently submitted to the NDA as an efficacy supplement (studies 308 and 313).[11] Based on the results of these trials, Tygacil was

[10] Id.

[11] Bergallo, C, A Jasovich, O Teglia, et al., 2009, Safety and efficacy of intravenous tigecycline in treatment of community-acquired pneumonia: results from a double-blind randomized phase 3 comparison study with

approved for the treatment of CABP in March 2009. The trials' co-primary endpoints were the clinical outcome at TOC visit for the CE and c-mITT populations. Noninferiority was concluded based on the lower limit of the 2-sided 95% CI greater than or equal to -15% (see Table 3).

Table 3: Clinical outcome of cure in CABP trials

Studies	Population	Tigecycline [a] n/N (%)	Levofloxacin [b] n/N (%)	95% CI [c]
308	CE	125/138 (90.6)	136/156 (87.2)	(-4.4, 11.2)
	c-mITT	149/191 (78.0)	158/203 (77.8)	(-8.5, 8.9)
313	CE	128/144 (88.9)	116/136 (85.3)	(-4.5, 11.8)
	c-mITT	170/203 (83.7)	163/200 (81.5)	(-5.5,9.6)

[a] 100 mg initially, followed by 50 mg every 12 hours.
[b] Levofloxacin 500 mg every 24 hours (or every 12 hours based on investigator's discretion in trial 313).
[c] 95% confidence intervals for the difference in clinical cure rates.

There was no overall imbalance (i.e., no increase in mortality observed between study arms, although the number of deaths was not identical) in all-cause mortality in the CABP trials. Twenty-three subjects (2.7%) died in the combined CABP trials (308 and 313): 12 (2.8%) in the tigecycline group and 11 (2.6%) in the levofloxacin group. Review of serious adverse events (SAEs) did not reveal an imbalance in the total number of SAEs or in individual SAEs.

We agree that higher rates of several infection-related adverse events were observed in the tigecycline arm in the cIAI trials. The review of the trials indicated that the main difference appeared to be related to reports of sepsis/septic shock in patients with intestinal perforation (in six tigecycline-treated patients and two imipenem-treated patients). The following warning was included in the WARNINGS AND PRECAUTIONS section of the Tygacil labeling:

> 5.9 Patients With Intestinal Perforation
>
> Caution should be exercised when considering TYGACIL monotherapy in patients with complicated intra-abdominal infections (cIAI) secondary to clinically apparent intestinal perforation. In cIAI studies (n=1642), 6 patients treated with TYGACIL and 2 patients treated with imipenem/cilastatin presented with intestinal perforations and developed sepsis/septic shock. The 6 patients treated with TYGACIL had higher APACHE II scores (median = 13) versus the 2 patients treated with imipenem/cilastatin (APACHE II scores = 4 and 6). Due to differences in baseline APACHE II scores between treatment groups and small overall numbers, the relationship of this outcome to treatment cannot be established.[12]

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levofloxacin, *Diagn Microbiol Infect Dis*, 63(1):52-61; Tanaseanu, C, C Bergallo, O Teglia, et al., 2008, Integrated results of 2 phase 3 studies comparing tigecycline and levofloxacin in community-acquired pneumonia, *Diagn Microbiol Infect Dis*, 61(3):329-338; Tanaseanu C, S Milutinovic, PI Calistru, et al., 2009, Efficacy and safety of tigecycline versus levofloxacin for community-acquired pneumonia, *BMC Pulm Med*, 9:44.

[12] A similar statement appeared in the "Precautions" section of the original Tygacil labeling approved on June 15, 2005.

We agree that nausea and vomiting were observed at higher rates in all tigecycline trials. However, nausea and vomiting are well known tigecycline adverse reactions and are described in the ADVERSE REACTIONS section of the Tygacil labeling.

In sum, we do not agree with your assertion that serious safety signals related to Tygacil were readily apparent from the clinical trials that supported approval for cSSSI and cIAI. The difference in number of deaths for tigecycline and comparator patients was noted and thoroughly investigated in the original NDA submission. However, substantial evidence of efficacy for the approved indications (cSSSI and cIAI) had been provided, and at that time there was no basis for concluding that this imbalance in the number of deaths was more than a chance finding.

2. FDA 2010 Pooled Analysis

In 2010, FDA conducted a pooled analysis of randomized clinical trials testing the safety and efficacy of tigecycline. You conclude that this analysis demonstrated a higher mortality with tigecycline relative to comparators (Petition at 5). You state that overall, for all trials combined, deaths occurred in 4.0% (150/3788) of subjects receiving tigecycline and 3.0% (110/3646) of subjects receiving comparator antibiotics (Id.). You also state that FDA's analysis revealed a statistically significant adjusted risk difference of 0.6% (95% CI: 0.1, 1.2) for all-cause mortality between tigecycline- and comparator-treated subjects, based on a random effects model stratified by trial weight (Id.). Lastly, you state that although the mortality difference was not statistically significant for each infection type, it was numerically greater in every infection type, particularly in HAP and VAP (Id.).

We agree with your statements that overall, for all trials combined, deaths occurred in 4.0% (150/3788) of subjects receiving tigecycline and 3.0% (110/3646) of subjects receiving comparator antibacterial drugs. We also agree that FDA's analysis revealed a statistically significant adjusted risk difference of 0.6% (95% CI: 0.1, 1.2) for all-cause mortality between tigecycline and comparator-treated subjects, based on a random effects model stratified by trial weight, and that although the mortality difference was not statistically significant for each infection type, it was numerically greater in every infection type, particularly in HAP and VAP. These data were added to the Tygacil labeling in 2010 and are also presented here in Table 4. We note that this FDA 2010 pooled analysis included clinical trials in patients with HAP, VAP, and DFI. Tygacil failed to demonstrate efficacy for these indications, and these are not approved indications for Tygacil.

Table 4: Patient deaths according to infection type in a pooled analysis of 13 clinical trials

Infection Type	Tigecycline deaths / total patients (%)	Comparator antibacterial drug deaths / total patients (%)	Risk Difference* (95% Confidence Interval)
cSSSI	12/834 (1.4%)	6/813 (0.7%)	0.7 (-0.3, 1.7)
cIAI	42/1382 (3.0%)	31/1393 (2.2%)	0.8 (-0.4, 2.0)
CAP	12/424 (2.8%)	11/422 (2.6%)	0.2 (-2.0, 2.4)
HAP	66/467 (14.1%)	57/467 (12.2%)	1.9 (-2.4, 6.3)
Non-VAP†	41/336 (12.2%)	42/345 (12.2%)	0.0 (-4.9, 4.9)
VAP†	25/131 (19.1%)	15/122 (12.3%)	6.8 (-2.1, 15.7)
RP	11/128 (8.6%)	2/43 (4.7%)	3.9 (-4.0, 11.9)

DFI	7/553 (1.3%)	3/508 (0.6%)	0.7 (-0.5, 1.8)
Overall Pooled	150/3788(4.0%)	110/3646 (3.0%)	0.6 (0.1,1.2)**

cSSSI = Complicated skin and skin structure infections; cIAI = Complicated intra-abdominal infections; CAP = Community-acquired pneumonia; HAP = Hospital-acquired pneumonia; VAP = Ventilator-associated pneumonia; RP = Resistant pathogens; DFI = Diabetic foot infections.
*Risk Difference = the difference between the percentage of patients who died in the Tygacil and comparator antibacterial drug groups. The 95% CI for each infection type was calculated using the normal approximation method without continuity correction.
†Subgroups of the HAP population.
**Overall adjusted (random effects model by trial weight) risk difference estimate.

3. July 2010 Labeling Revision

In July 2010, the Tygacil labeling was revised to include information on all-cause mortality, mortality imbalance, and lower cure rates in VAP in light of results from the FDA pooled analysis of clinical trials described above. In addition to the Tygacil labeling changes, FDA issued a drug safety communication with this information.[13]

As a result of the revision, the all-cause mortality and mortality imbalance subsections of the WARNINGS AND PRECAUTIONS section of the Tygacil labeling read:

> 5.1 All-Cause Mortality
>
> An increase in all-cause mortality has been observed across Phase 3 and 4 clinical trials in TYGACIL-treated patients versus comparator-treated patients. In all 13 Phase 3 and 4 trials that included a comparator, death occurred in 4.0% (150/3788) of patients receiving TYGACIL and 3.0% (110/3646) of patients receiving comparator drugs. In a pooled analysis of these trials, based on random effects model by trial weight, an adjusted risk difference of all-cause mortality was 0.6% (95% CI 0.1, 1.2) between TYGACIL and comparator-treated patients. The cause of this increase has not been established. This increase in all-cause mortality should be considered when selecting among treatment options. *[see Warnings and Precautions (5.4) and Adverse Reactions (6.1)].*
>
> 5.4 Mortality Imbalance and Lower Cure Rates in Ventilator-Associated Pneumonia
>
> A trial of patients with hospital acquired pneumonia failed to demonstrate the efficacy of TYGACIL. In this trial, patients were randomized to receive TYGACIL (100 mg initially, then 50 mg every 12 hours) or a comparator. In addition, patients were allowed to receive specified adjunctive therapies. The sub-group of patients with ventilator-associated pneumonia who received TYGACIL had lower cure rates (47.9% versus 70.1% for the clinically evaluable population).
>
> In this trial, greater mortality was seen in patients with ventilator-associated pneumonia who received TYGACIL (25/131 [19.1%] versus 15/122 [12.3%] in comparator-treated patients) *see Adverse Reactions (6.1)]*. Particularly high mortality was seen among TYGACIL-treated patients with ventilator-associated pneumonia and bacteremia at baseline (9/18 [50.0%] versus 1/13 [7.7%] in comparator-treated patients).

[13] FDA Drug Safety Communication: Increased risk of death with Tygacil (tigecycline) compared to other antibiotics used to treat similar infections, September 2010, http://www.fda.gov/Drugs/DrugSafety/ucm224370.htm.

FDA's September 2010 drug safety communication alerted the public about increased mortality risk associated with Tygacil along with information on the FDA pooled analysis that resulted in the 2010 Tygacil label changes and drug safety communication.[14]

At that time, we believed that there was some indication that the increase in mortality might be associated with a decreased effectiveness resulting in progression of the infection. We also believed that there might be more cardiac adverse events in the tigecycline group. For this reason, we required the Tygacil NDA holder to conduct a thorough QT study as a post-marketing requirement in July 2010.[15] A QT study assesses the potential of a drug to prolong a QT interval on electrocardiography (ECG), which may indicate that the drug can cause fatal cardiac arrhythmias. The NDA holder submitted the final report of the QT study in October 2011. The results of this study indicate that the use of tigecycline is not likely to be associated with an increased risk of fatal cardiac arrhythmias.

4. Post 2010 Meta-Analyses

In the Petition, you argue that several meta-analyses conducted after the July 2010 labeling revision also support the addition of a boxed warning.

a. Yahav et al. Meta-Analysis

You state that recently published systematic review and meta-analysis by Yahav et al. showed a higher overall mortality rate for tigecycline than for comparator antibiotics (Petition at 6). You state that the Yahav et al. meta-analysis confirms findings from FDA's 2010 pooled analysis (Id.). You point to a statement in the Yahav et al. publication that poorer clinical antibacterial efficacy, rather than fatal adverse events, is the likely explanation for their results (Petition at 8). You also note a list of what you assess to be other key data from the Yahav et al. meta-analysis on page 7 of the Petition (Petition at 7). Lastly, you state that FDA's pooled analysis and the Yahav et al. meta-analysis demonstrate 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 (Petition at 2).

The publication by Yahav et al. reports a statistically significantly higher overall mortality for patients treated with tigecycline compared with the comparator-treated patients in a meta-analysis of 13 tigecycline trials with no significant increase in mortality in individual indications.[16] As mentioned above, the FDA pooled analysis demonstrated an adjusted risk difference of all-cause mortality of 0.6% (95% CI: 0.1, 1.2) between tigecycline and comparator-treated patients. Therefore, we agree with your statement that both analyses showed an increase in all-cause mortality in the tigecycline arm. Like the 2010 FDA pooled analysis, we note that

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[14] Id.

[15] Supplement Approval Letter for NDA 021821, from Dr. Sumathi Nambiar, Deputy Director for Safety, Division of Anti-Infective and Ophthalmology Products, Office of Antimicrobial Products, Center for Drug Evaluation and Research, FDA, to Dr. Nia Tatsis, Senior Manager, Pfizer Pharmaceuticals, Inc. (July 16, 2010), available at: http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/021821s021,021821s025,021821s027ltr.pdf.

[16] Yahav, D, A Lador, M Paul, et al., 2011, Efficacy and safety of tigecycline: a systematic review and meta-analysis, *J Antimicrob Chemother*, 66(9):1963-1971.

the Yahav et al. analysis included clinical trials enrolling patients with HAP and DFI, and Tygacil is not approved for these indications.

Citing both the 2010 FDA pooled analysis and the Yahav et al. analysis, you state that these analyses showed that overall risk of death in subjects treated with tigecycline was approximately 20 to 30% higher than in subjects treated with comparator antibacterial drugs (Petition at 2). This statement is correct but is subject to misinterpretation as it fails to provide the absolute difference in the risk of death. In the Petition, you use relative risk increase to describe the overall risk of death with tigecycline. Relative measures of risk do not account for baseline mortality, and tend to overstate the risk of mortality when baseline mortality is not high. Under this circumstance, absolute risk measures accounting for the baseline mortality rate represent a more appropriate quantification of mortality risk. For example, the mortality rate in 13 comparative tigecycline trials included in the 2010 FDA pooled analysis was 4.0% in the tigecycline and 3.0% in comparator arms which translates to an absolute risk increase in tigecycline mortality of 1% and an adjusted risk difference for mortality stratified by trial weight of 0.6% (95% CI 0.1, 1.2).

b. Prasad et al. Meta-Analysis

You also point to a recently published meta-analysis by Prasad et al., which you state reaffirms the results of the FDA pooled analysis and the Yahav et al. meta-analysis (Petition Supplement at 2). You state that the Prasad el al. meta-analysis found that across ten published and three unpublished randomized controlled trials, tigecycline was associated with increased mortality, with an absolute risk difference (RD) of 0.7% (95% CI, 0.1%-1.2%, P = .01) as well as increased non-cure rates (RD, 2.9%; 95% CI: 0.6%-5.2%; P = 0.01) (Petition Supplement at 2-3).

The results of the Prasad et al. meta-analysis are consistent with the FDA pooled analysis, which showed that the adjusted risk difference for mortality associated with tigecycline was 0.6%. We note that the Prasad et al. meta-analysis included trials enrolling patients with HAP and DFI, conditions for which Tygacil has not been demonstrated to be efficacious. As cure is assessed differently depending upon the disease studied, pooled analyses of cure rates may not be statistically appropriate for purposes of these analyses.

c. Other Recently Published Meta-Analyses

Lastly, you mention two other recently published meta-analyses that failed to show that tigecycline-treated subjects had significantly increased mortality in comparison to subjects receiving comparator antibiotics (Petition at 8).[17] You conclude that these meta-analyses used incomplete data, with one reporting results on only eight published studies and the other lacking complete mortality data for two unpublished studies (Id.).

[17] Cai, Y, R Wang, B Liang, et al., 2011, Systematic review and meta-analysis of the effectiveness and safety of tigecycline for treatment of infection disease, *Antimicrob Agents Chemother*, 55:1162-72; Tasina, E, AB Haidich, S Kokkali, et al., 2011, Efficacy and safety of tigecycline for the treatment of infectious diseases: a meta-analysis, *Lancet Infect Dis*, published online July 25; DOI:10.1016/S1473-3099(11)70177-3.

We agree with your conclusions that these studies used incomplete data. The Cai et al. meta-analysis included mortality data for only seven out of thirteen comparative tigecycline clinical trials and did not include HAP and DFI trials. The Tasina et al. meta-analysis did not have mortality data for one phase 4 trial of cSSSI and had incomplete mortality data for the DFI trial.

5. Recent Labeling Changes

As noted, in July 2010, the Tygacil label was revised to include information on all-cause mortality, mortality imbalance, and lower cure rates in VAP in light of results from a pooled analysis of clinical trials by FDA. Our review of all reported deaths in fourteen pre-and post-approval tigecycline trials that had been conducted up to that point did not allow us to definitively determine specific causes associated with the increase in mortality. Therefore, at the time of the July 2010 labeling revision, there was no additional information to add to the Tygacil labeling on mortality imbalance other than what was already included in the revised labeling.

As also mentioned above, in July 2010 we required the Tygacil NDA holder to conduct a thorough QT study as a post-marketing requirement, and the NDA holder submitted the final report of the QT study in October 2011. The NDA holder concluded that single doses of tigecycline at 50 mg and 200 mg in healthy volunteers did not demonstrate a QTc effect, and single doses of moxifloxacin 400 mg (the positive control) established that the study had adequate assay sensitivity to detect an increase in QTc. The results of this study indicate that the use of tigecycline is not likely to be associated with an increased risk of torsades de pointes or ventricular tachycardia. The evidence does not suggest that the increase in mortality in tigecycline trials is attributable to this form of cardiotoxicity secondary to tigecycline.

FDA also conducted additional analyses of information collected in tigecycline clinical trials following the July 2010 labeling changes. These analyses found that an increased risk in tigecycline-associated mortality was observed not only in non-approved but also in approved Tygacil indications. An analysis of mortality in all trials conducted for approved indications (cSSSI, cIAI, and CABP), including post-market trials, showed the adjusted risk difference for mortality of 0.6% (95% CI 0.0, 1.2). A separate analysis of mortality in the trials used to support Tygacil approval for the cSSSI (Studies 300 and 305), cIAI (Studies 301 and 306), and CABP (Studies 308 and 313) indications was also conducted. The overall mortality rates in these trials were 2.4% in the tigecycline group and 1.8% in the comparator group. The adjusted risk difference for mortality stratified by trial weight was 0.5% (95% CI -0.2, 1.2).

The increase in mortality observed in post-market trials conducted for approved indications, gave the Agency reason to consider labeling revisions. Based on the results of FDA's latest analyses, on September 26, 2013, we approved further revisions to the Tygacil labeling.[18]

[18] Language that was added to the Tygacil labeling, aside from the boxed warning, is underlined. The boxed warning in its entirety is new.

The Tygacil labeling now has a boxed warning that reads as follows:

> WARNING: ALL-CAUSE MORTALITY
>
> An increase in all-cause mortality has been observed in a meta-analysis of Phase 3 and 4 clinical trials in TYGACIL-treated patients versus comparator. The cause of this mortality risk difference of 0.6% (95% CI 0.1, 1.2) has not been established. TYGACIL should be reserved for use in situations when alternative treatments are not suitable *[see Indications and Usage (1.4), Warnings and Precautions (5.1, 5.2) and Adverse Reactions (6.1)]*.

The WARNINGS AND PRECAUTIONS section of the Tygacil labeling now states:

> 5.1 All-Cause Mortality
>
> An increase in all-cause mortality has been observed in a meta-analysis of Phase 3 and 4 clinical trials in TYGACIL-treated patients versus comparator-treated patients. In all 13 Phase 3 and 4 trials that included a comparator, death occurred in 4.0% (150/3788) of patients receiving TYGACIL and 3.0% (110/3646) of patients receiving comparator drugs. In a pooled analysis of these trials, based on a random effects model by trial weight, the adjusted risk difference of all-cause mortality was 0.6% (95% CI 0.1, 1.2) between TYGACIL and comparator-treated patients. An analysis of mortality in all trials conducted for approved indications (cSSSI, cIAI, and CABP), including post-market trials showed an adjusted mortality rate of 2.5% (66/2640) for tigecycline and 1.8% (48/2628) for comparator, respectively. The adjusted risk difference for mortality stratified by trial weight was 0.6% (95% CI 0.0, 1.2).
>
> The cause of this mortality difference has not been established. Generally, deaths were the result of worsening infection, complications of infection or underlying co-morbidities. TYGACIL should be reserved for use in situations when alternative treatments are not suitable *[see Indications and Usage (1.4), Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*.

Also, the following paragraph has also been added to the ADVERSE REACTIONS section of the Tygacil label under subsection 6.1 Clinical Trials Experience:

> An analysis of mortality in all trials for approved indications – cSSSI, cIAI, and CABP, including post-market trials (315, 316, 400, 900) – showed an adjusted mortality rate of 2.5% (66/2640) for tigecycline and 1.8% (48/2648) for comparator, respectively. The adjusted risk difference for mortality stratified by trial weight was 0.6% (95% CI 0.0, 1.2).

Further, the INDICATIONS AND USAGE section has been revised to state:

> 1.4 Limitations of Use
>
> TYGACIL is not indicated for the treatment of diabetic foot infections. A clinical trial failed to demonstrate non-inferiority of TYGACIL for treatment of diabetic foot infections.
>
> TYGACIL is not indicated for the treatment of hospital acquired or ventilator-associated pneumonia. In a comparative clinical trial, greater mortality and decreased efficacy were reported in TYGACIL-treated patients *[see Warnings (5.4)]*.
>
> To reduce the development of drug-resisted bacteria and maintain the effectiveness of TYGACIL and other antibacterial drugs, TYGACIL should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selection or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.
>
> Appropriate specimens for bacteriological examination should be obtained in order to isolate and identify the causative organisms and to determine their susceptibility to tigecycline. TYGACIL may be initiated as empiric monotherapy before results of these tests are known.

You request that FDA add language to a boxed warning indicating that Tygacil 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 (Petition at 1). As described above, the boxed warning which has been added to the label includes the statement, "Tygacil should be reserved for use in situations when alternative treatments are not suitable." This statement has addressed your request for a boxed warning recommendation that tigecycline should be used only as a last-resort antibacterial drug.

The language you request (that "Tygacil should be used as a last-resort antibiotic for serious infections") may imply that the drug should be used in patients with the most severe infections. (See Petition at 10). However, increased mortality in patients treated with tigecycline was seen most clearly in patients with severe infections such as VAP, and an FDA drug safety communication advises use of alternatives to tigecycline in patients with severe infections.[19] As mentioned above, FDA considers Tygacil to be an appropriate option for its approved indications in situations when alternative treatments are not suitable.

We believe language regarding the use of Tygacil in combination with one or more bactericidal antibacterial drugs is not appropriate in light of the Agency's current conclusions and

[19] FDA Drug Safety Communication: Increased risk of death with Tygacil (tigecycline) compared to other Antibacterial drugs used to treat similar infections, Sept. 2010, http://www.fda.gov/Drugs/DrugSafety/ucm224370.htm.

recommendations regarding Tygacil use. The use of tigecycline always in combination with one or more antibacterial drugs with bactericidal activity has not been studied in clinical trials reviewed by FDA and therefore should not be recommended in labeling. Moreover, such a recommendation may lead to unnecessary antibacterial drug exposure, higher adverse events and resistance rates. In addition, as a bacteriostatic inhibitor of microbial protein synthesis, tigecycline may antagonize bactericidal effects of other antibacterial drugs such as beta-lactams and aminoglycosides.[20,21]

In sum, your request that information about an increase in mortality be presented as a boxed warning is granted based on our additional analyses. Your request that FDA add a statement to the boxed warning that Tygacil should only be used as a last resort antibiotic has been addressed by the boxed warning added to the Tygacil labeling on September 26, 2013 which states, "Tygacil should be reserved for use in situations when alternative treatments are not suitable." Your request that FDA add a statement to the boxed warning that Tygacil should be only used in combination with one or more bactericidal antibiotics is denied.

B. Request to Distribute an FDA-Approved Medication Guide

In the Petition, you request that FDA require the distribution of an FDA-approved patient Medication Guide containing a warning about the increased risk of death and the need for restricted use, which you also argue should be added to a boxed warning on Tygacil labeling, as discussed above (Petition at 2). You request that this Medication Guide be dispensed prior to the administration of the first dose of a course of Tygacil (Petition at 2).

Your request to require the distribution of a Medication Guide warning about an increased risk of death and the need for the restricted use of Tygacil is not granted, because we believe that a Medication Guide is not necessary for the safe and effective use of the drug product. Title 21 Part 208 of the Code of Federal Regulations (21 CFR 208.1-208.26) sets forth requirements for Medication Guides for human prescription drug products that the Agency determines pose a serious and significant public health concern and require distribution of FDA-approved patient information. The purpose of Medication Guides, as specified by regulation, "is to provide information when the FDA determines in writing that it is necessary to patients' safe and effective use of drug products" (21 CFR 208.1(b)).

Under section 208.1(c), Medication Guides will be required if FDA determines at least one of three circumstances described in the regulation has been met. We summarize below the applicability of each circumstance described in the regulation to your request for a Medication Guide.

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[20] Lepper MH, Dowling HF. Treatment of pneumococcic meningitis with penicillin compared with penicillin plus aureomycin; studies including observations on an apparent antagonism between penicillin and aureomycin. *AMA Arch Intern Med.* Oct 1951; 88(4):489-94.

[21] Strom J. The question of antagonism between penicillin and chlortetracycline, illustrated by therapeutical experiments in scarlatina. *Antibiotic Med Clin Ther.* Jan 1955; 1(1):6-12.

> Circumstance (1): The drug product is one for which patient labeling could help prevent serious adverse effects.[22]

The serious adverse effect for which you asked that FDA require a Medication Guide is increased risk of death. Patient labeling, however, is not likely to prevent increased mortality associated with Tygacil as there is no specific preventive measure that can be taken by the patient to decrease the risk of higher mortality.

> Circumstance (2): The drug product is one that has serious risk(s) (relative to benefits) or which patients should be made aware because information concerning the risk(s) could affect patients' decisions to use, or to continue to use, the product.[23]

Because tigecycline is primarily administered in the hospital setting or an outpatient center by a health care provider, the health care provider is in the best position to educate patients about the risks and benefits of tigecycline. We note that the new boxed warning added to labeling includes the statement, "Tygacil should be reserved for use in situations when alternative treatments are not suitable." In addition, the Warnings and Precautions section of the labeling was revised to describe the mortality imbalance. Health care providers can consider this information and discuss the use of this drug with the patient, taking into consideration the patient's infection and individual medical condition. FDA has advised that "health care providers who directly communicate with patients are in the best position to educate patients by personalizing oral and written information."[24] We believe that the risk information provided in the newly approved Tygacil labeling, along with counseling by the health care provider administering the drug, are sufficient to allow the patient to make an informed decision whether to use, or to continue to use, tigecycline.

> Circumstance (3): The drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.[25]

Patients generally do not self-administer tigecycline. Accordingly, patient adherence to tigecycline directions for use would not be increased by distributing a Medication Guide and lack of patient adherence to directions for use is not relevant to the effectiveness of tigecycline.

For these reasons, your request to distribute an FDA-approved patient Medication Guide for Tygacil is denied.

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[22] The Agency stated in the preamble to the final rule on *Prescription Drug Labeling Medication Guide Requirements* (63 FR 66378, December 1, 1998) (Medication Guide Final Rule) that drugs potentially falling into this category are those "cases in which there is a known 'risk control strategy'" or "where easily taken preventive measures can prevent harm" (Medication Guide Final Rule at 66388).

[23] The Agency stated that drugs potentially meeting this criterion would be those in which "the risk of a drug is relatively great, greater than a patient would anticipate given the relatively benign condition being treated…[or] where understanding the adverse effects is critical to a choice among alternative treatments with different safety and effectiveness profiles…." (Id. at 66388).

[24] Id. at 66384. FDA added that "the final regulations will require that manufacturers develop and disseminate patient information *only for selected medications* that the agency has determined cannot be used safely and effectively without patient information" (Id. (emphasis added)).

[25] The Agency stated that drugs potentially falling into this category are those for which "nonadherence could compromise patients' health by interfering with effectiveness" (Id. at 66388).

C. Request to Require Pfizer to Distribute a Dear Doctor Letter

In the Petition, you request that FDA require Pfizer distribute a Dear Doctor letter alerting physicians about increased mortality risk and need for restricted use of Tygacil (Petition at 2).

Pfizer has voluntarily issued a DHCP letter regarding the most recent Tygacil labeling changes. The Agency has also posted a drug safety communication with information about the recent labeling changes on our Web site at http://www.fda.gov/Drugs/DrugSafety/ucm369580.htm.

Since both Pfizer and FDA have already informed health care professionals and the public of the labeling changes, your request to require a Dear Doctor letter is moot and is therefore denied.

III. CONCLUSION

Based on the reasons described in this response, we grant in part and deny in part your requests. As with all drug products, we will continue to monitor the safety of Tygacil and take further action if we determine it is appropriate.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research