

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
21-821/S026/S031

Trade Name: Tygacil

Generic Name: tigecycline

Sponsor: PF PRISM C.V.

Approval Date: 9/26/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
21-821/S026/S031

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-821/S026/S031

APPROVAL LETTER



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-821/S-026 and S-031

SUPPLEMENT APPROVAL

PF PRISM C.V.
c/o Pfizer Inc.
Attention: Nadia Kirzecky
Director, Worldwide Safety and Regulatory
235 East 42nd Street
New York, NY 10017-5755

Dear Ms. Kirzecky:

Please refer to your Supplemental New Drug Applications (sNDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

NDA#/Drug Name	Supplement Number	Submission Date	Date Received
NDA 21-821/Tygacil (tigecycline) for Injection	S-026	September 30, 2009	September 30, 2009
	S-031	February 11, 2011	February 11, 2011

We acknowledge receipt of your amendments to these supplemental applications dated November 29, 2011, February 7, 2012 [S-031 only], and February 13, July 3, and September 23, 2013.

Supplemental application S-026 is a “Prior Approval” supplement that provides for changes to the **INDICATIONS AND USAGE** section stating that Tygacil is not indicated for the treatment of diabetic foot infections.

Supplemental application S-031 is a “Changes Being Effected” supplement that provides for changes to the **ADVERSE REACTIONS** section of the labeling to include the adverse reactions of pneumonia and severe skin reactions, including Stevens-Johnson syndrome.

In addition to the changes requested in the above supplements, the attached labeling also includes the following changes as discussed with you via multiple electronic communications (e-mails) and finalized in your submission containing revised draft labeling on September 23, 2013.

- Addition of a “**BOXED WARNING**” to include information from meta-analysis of clinical trials that showed an increased risk of mortality in Tygacil-treated patients and to reserve Tygacil for use in situations when alternative treatments are not suitable.
- Addition of **Limitations of Use** (1.4) to include information that Tygacil is not indicated for the treatment of diabetic foot infections and hospital-acquired or ventilator-associated pneumonia.
- Revisions of the **DOSAGE AND ADMINISTRATION** section (2), **Pediatric Patients** subsection (2.3) and **USE IN SPECIFIC POPULATIONS** section (8.0), **Pediatric Use** subsection (8.4) to include information about use in the pediatric population.
- Revisions to the **WARNINGS AND PRECAUTIONS** section (5), **All-Cause Mortality** subsection (5.1) regarding the increased risk of mortality.
- The following revisions to the **ADVERSE REACTIONS** section (6):
 - **Clinical Trials Experience** subsection (6.1) to include information about an increase in mortality in trials conducted for approved indications
 - **Post-Marketing Experience** subsection (6.2), to include adverse reactions of Stevens-Johnson syndrome and symptomatic hypoglycemia
 - Revised the incidence of adverse reactions in Table 1.
- Addition of a **Pharmacodynamics** subsection (12.2), **Cardiac Electrophysiology**, to the **CLINICAL PHARMACOLOGY** section (12).
- Minor editorial changes including updates to the **REFERENCES** (15) section.

APPROVAL & LABELING

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling text for package insert, with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in these supplemental applications, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

PROMOTIONAL MATERIALS

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Carmen DeBellas, PharmD, R.Ph., Regulatory Project Manager, at (301) 796-1203.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Acting Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUMATHI NAMBIAR
09/26/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-821/S026/S031

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TYGACIL safely and effectively. See full prescribing information for TYGACIL.

TYGACIL® (tigecycline) FOR INJECTION for intravenous use

Initial U.S. Approval: 2005

WARNING: ALL-CAUSE MORTALITY

See full prescribing information for complete boxed warning.

All-cause mortality was higher in patients treated with TYGACIL than comparators in a meta-analysis of clinical trials. 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)*].

To reduce the development of drug-resistant 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 bacteria.

RECENT MAJOR CHANGES

Boxed Warning	09/2013
Indications and Usage, Limitations of Use (1.4)	09/2013
Dosage and Administration, Preparation and Handling (2.4)	11/2012
Warnings and Precautions, All-Cause Mortality (5.1)	09/2013

INDICATIONS AND USAGE

TYGACIL is a tetracycline-class antibacterial drug indicated in patients 18 years of age and older for:

- Complicated skin and skin structure infections (1.1)
- Complicated intra-abdominal infections (1.2)
- Community-acquired bacterial pneumonia (1.3)

Limitations of Use: TYGACIL is not indicated for treatment of diabetic foot infection or hospital-acquired pneumonia, including ventilator-associated pneumonia (1.4).

DOSAGE AND ADMINISTRATION

- Initial dose of 100 mg, followed by 50 mg every 12 hours administered intravenously over approximately 30 to 60 minutes. (2.1)
- Severe hepatic impairment (Child Pugh C): Initial dose of 100 mg followed by 25 mg every 12 hours. (2.2)

DOSAGE FORMS AND STRENGTHS

50 mg lyophilized powder for reconstitution in a single-dose 5 mL vial or 10 mL vial. (3)

CONTRAINDICATIONS

- Known hypersensitivity to tigecycline. (4)

WARNINGS AND PRECAUTIONS

- A meta-analysis of Phase 3 and 4 clinical trials demonstrated an increase in all-cause mortality in TYGACIL-treated patients compared to controls with a risk difference of 0.6% (95% CI 0.1, 1.2). The cause of this increase has not been established. An increase was also seen in a meta-analysis limited to the approved indications [0.6% (95% CI 0.0, 1.2)]. The greatest difference in mortality was seen in TYGACIL-treated patients with ventilator-associated pneumonia (5.1, 5.2).
- Anaphylaxis/anaphylactoid reactions have been reported with TYGACIL, and may be life-threatening. Exercise caution in patients with known hypersensitivity to tetracyclines. (5.3)
- Hepatic dysfunction and liver failure have been reported with TYGACIL. (5.4)
- Pancreatitis, including fatalities, has been reported with TYGACIL. If pancreatitis is suspected, then consider stopping TYGACIL. (5.5)
- TYGACIL may cause fetal harm when administered to a pregnant woman. (5.6)
- The use of TYGACIL during tooth development may cause permanent discoloration of the teeth. (5.7)
- *Clostridium difficile* associated diarrhea: evaluate if diarrhea occurs. (5.8)

ADVERSE REACTIONS

The most common adverse reactions (incidence >5%) are nausea, vomiting, diarrhea, abdominal pain, headache, and increased SGPT. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Wyeth Pharmaceuticals Inc. at 1-800-934-5556 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- Suitable anticoagulation test should be monitored if TYGACIL is administered to patients receiving warfarin. (7.1)

USE IN SPECIFIC POPULATIONS

- Pediatrics: Use in patients under 18 years of age is not recommended. Pediatric trials were not conducted because of the higher risk of mortality seen in adult trials (8.4)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 09/2013

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FULL PRESCRIBING INFORMATION

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)*].

1 INDICATIONS AND USAGE

TYGACIL is a tetracycline-class antibacterial drug indicated for the treatment of infections caused by susceptible isolates of the designated microorganisms in the conditions listed below for patients 18 years of age and older:

1.1 Complicated Skin and Skin Structure Infections

Complicated skin and skin structure infections caused by *Escherichia coli*, *Enterococcus faecalis* (vancomycin-susceptible isolates), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus agalactiae*, *Streptococcus anginosus* grp. (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), *Streptococcus pyogenes*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, and *Bacteroides fragilis*.

1.2 Complicated Intra-abdominal Infections

Complicated intra-abdominal infections caused by *Citrobacter freundii*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Enterococcus faecalis* (vancomycin-susceptible isolates), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus anginosus* grp. (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), *Bacteroides fragilis*, *Bacteroides thetaiotaomicron*, *Bacteroides uniformis*, *Bacteroides vulgatus*, *Clostridium perfringens*, and *Peptostreptococcus micros*.

1.3 Community-Acquired Bacterial Pneumonia

Community-acquired bacterial pneumonia caused by *Streptococcus pneumoniae* (penicillin-susceptible isolates), including cases with concurrent bacteremia, *Haemophilus influenzae* (beta-lactamase negative isolates), and *Legionella pneumophila*.

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 and Precautions* (5.2)].

To reduce the development of drug-resistant 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 selecting 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.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosage and Administration

The recommended dosage regimen for TYGACIL is an initial dose of 100 mg, followed by 50 mg every 12 hours. Intravenous infusions of TYGACIL should be administered over approximately 30 to 60 minutes every 12 hours.

The recommended duration of treatment with TYGACIL for complicated skin and skin structure infections or for complicated intra-abdominal infections is 5 to 14 days. The recommended duration of treatment with TYGACIL for community-acquired bacterial pneumonia is 7 to 14 days. The duration of therapy should be guided by the severity and site of the infection and the patient's clinical and bacteriological progress.

2.2 Patients With Hepatic Impairment

No dosage adjustment is warranted in patients with mild to moderate hepatic impairment (Child Pugh A and Child Pugh B). In patients with severe hepatic impairment (Child Pugh C), the initial dose of TYGACIL should be 100 mg followed by a reduced maintenance dose of 25 mg every 12 hours. Patients with severe hepatic impairment (Child Pugh C) should be treated with caution and monitored for treatment response [see *Clinical Pharmacology* (12.3) and *Use in Specific Populations* (8.6)].

2.3 Pediatric Patients

The safety and efficacy of the proposed pediatric dosing regimens have not been evaluated due to the observed increase in mortality associated with tigecycline in adult patients. Tigecycline should not be used in pediatric patients unless no alternative antibacterial drugs are available. Under these circumstances, the following doses are suggested:

- Pediatric patients aged 8 to 11 years should receive 1.2 mg/kg of tigecycline every 12 hours intravenously to a maximum dose of 50 mg of tigecycline every 12 hours.

- Pediatric patients aged 12 to 17 years should receive 50 mg of tigecycline every 12 hours,

The proposed pediatric doses of tigecycline were chosen based on exposures observed in pharmacokinetic trials, which included small numbers of pediatric patients [*see Use in Specific Populations (8.4) and Clinical Pharmacology (12.3)*].

2.4 Preparation and Handling

Each vial of TYGACIL should be reconstituted with 5.3 mL of 0.9% Sodium Chloride Injection, USP, 5% Dextrose Injection, USP, or Lactated Ringer's Injection, USP to achieve a concentration of 10 mg/mL of tigecycline. (Note: Each vial contains a 6% overage. Thus, 5 mL of reconstituted solution is equivalent to 50 mg of the drug.) The vial should be gently swirled until the drug dissolves. Withdraw 5 mL of the reconstituted solution from the vial and add to a 100 mL intravenous bag for infusion (for a 100 mg dose, reconstitute two vials; for a 50 mg dose, reconstitute one vial). The maximum concentration in the intravenous bag should be 1 mg/mL. The reconstituted solution should be yellow to orange in color; if not, the solution should be discarded. Parenteral drug products should be inspected visually for particulate matter and discoloration (e.g., green or black) prior to administration. Once reconstituted, TYGACIL may be stored at room temperature (not to exceed 25°C/77°F) for up to 24 hours (up to 6 hours in the vial and the remaining time in the intravenous bag). If the storage conditions exceed 25°C (77°F) after reconstitution, tigecycline should be used immediately. Alternatively, TYGACIL mixed with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP may be stored refrigerated at 2° to 8°C (36° to 46°F) for up to 48 hours following immediate transfer of the reconstituted solution into the intravenous bag.

TYGACIL may be administered intravenously through a dedicated line or through a Y-site. If the same intravenous line is used for sequential infusion of several drugs, the line should be flushed before and after infusion of TYGACIL with 0.9% Sodium Chloride Injection, USP, 5% Dextrose Injection, USP or Lactated Ringer's Injection, USP. Injection should be made with an infusion solution compatible with tigecycline and with any other drug(s) administered via this common line.

Compatibilities

Compatible intravenous solutions include 0.9% Sodium Chloride Injection, USP, 5% Dextrose Injection, USP, and Lactated Ringer's Injection, USP. When administered through a Y-site, TYGACIL is compatible with the following drugs or diluents when used with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP: amikacin, dobutamine, dopamine HCl, gentamicin, haloperidol, Lactated Ringer's, lidocaine HCl, metoclopramide, morphine, norepinephrine, piperacillin/tazobactam (EDTA formulation), potassium chloride, propofol, ranitidine HCl, theophylline, and tobramycin.

Incompatibilities

The following drugs should not be administered simultaneously through the same Y-site as TYGACIL: amphotericin B, amphotericin B lipid complex, diazepam, esomeprazole and omeprazole.

3 DOSAGE FORMS AND STRENGTHS

Each single-dose 5 mL glass vial and 10 mL glass vial contain 50 mg of tigecycline as an orange lyophilized powder for reconstitution.

4 CONTRAINDICATIONS

TYGACIL is contraindicated for use in patients who have known hypersensitivity to tigecycline.

5 WARNINGS AND PRECAUTIONS

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)*].

5.2 Mortality Imbalance and Lower Cure Rates in Hospital-Acquired Pneumonia

A trial of patients with hospital acquired, including ventilator-associated, 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).

5.3 Anaphylaxis/Anaphylactoid Reactions

Anaphylaxis/anaphylactoid reactions have been reported with nearly all antibacterial agents, including TYGACIL, and may be life-threatening. TYGACIL is structurally similar to tetracycline-class antibiotics and should be administered with caution in patients with known hypersensitivity to tetracycline-class antibiotics.

5.4 Hepatic Effects

Increases in total bilirubin concentration, prothrombin time and transaminases have been seen in patients treated with tigecycline. Isolated cases of significant hepatic dysfunction and hepatic failure have been reported in patients being treated with tigecycline. Some of these patients were receiving multiple concomitant medications. Patients who develop abnormal liver function tests during tigecycline therapy should be monitored for evidence of worsening hepatic function and evaluated for risk/benefit of continuing tigecycline therapy. Adverse events may occur after the drug has been discontinued.

5.5 Pancreatitis

Acute pancreatitis, including fatal cases, has occurred in association with tigecycline treatment. The diagnosis of acute pancreatitis should be considered in patients taking tigecycline who develop clinical symptoms, signs, or laboratory abnormalities suggestive of acute pancreatitis. Cases have been reported in patients without known risk factors for pancreatitis. Patients usually improve after tigecycline discontinuation. Consideration should be given to the cessation of the treatment with tigecycline in cases suspected of having developed pancreatitis [*see Adverse Reactions (6.2)*].

5.6 Use During Pregnancy

TYGACIL may cause fetal harm when administered to a pregnant woman. If the patient becomes pregnant while taking tigecycline, the patient should be apprised of the potential hazard to the fetus. Results of animal studies indicate that tigecycline crosses the placenta and is found in fetal tissues. Decreased fetal weights in rats and rabbits (with associated delays in ossification) and fetal loss in rabbits have been observed with tigecycline [*see Use in Specific Populations (8.1)*].

5.7 Tooth Development

The use of TYGACIL during tooth development (last half of pregnancy, infancy, and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). Results of studies in rats with TYGACIL have shown bone discoloration. TYGACIL should not be used during tooth development unless other drugs are not likely to be effective or are contraindicated.

5.8 *Clostridium difficile* Associated Diarrhea

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including TYGACIL, and may range in severity from mild diarrhea to fatal

colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

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.

5.10 Tetracycline-Class Effects

TYGACIL is structurally similar to tetracycline-class antibiotics and may have similar adverse effects. Such effects may include: photosensitivity, pseudotumor cerebri, and anti-anabolic action (which has led to increased BUN, azotemia, acidosis, and hyperphosphatemia). As with tetracyclines, pancreatitis has been reported with the use of TYGACIL [see *Warnings and Precautions* (5.5)].

5.11 Superinfection

As with other antibacterial drugs, use of TYGACIL may result in overgrowth of non-susceptible organisms, including fungi. Patients should be carefully monitored during therapy. If superinfection occurs, appropriate measures should be taken.

5.12 Development of Drug-Resistant Bacteria

Prescribing TYGACIL in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In clinical trials, 2514 patients were treated with TYGACIL. TYGACIL was discontinued due to adverse reactions in 7% of patients compared to 6% for all comparators. Table 1 shows the incidence of treatment-emergent adverse reactions through test of cure reported in $\geq 2\%$ of patients in these trials.

Table 1. Incidence (%) of Adverse Reactions Through Test of Cure Reported in $\geq 2\%$ of Patients Treated in Clinical Studies

Body System Adverse Reactions	TYGACIL (N=2514)	Comparators ^a (N=2307)
Body as a Whole		
Abdominal pain	6	4
Abscess	2	2
Asthenia	3	2
Headache	6	7
Infection	7	5
Cardiovascular System		
Phlebitis	3	4
Digestive System		
Diarrhea	12	11
Dyspepsia	2	2
Nausea	26	13
Vomiting	18	9
Hemic and Lymphatic System		
Anemia	5	6
Metabolic and Nutritional		
Alkaline Phosphatase Increased	3	3
Amylase Increased	3	2
Bilirubinemia	2	1
BUN Increased	3	1
Healing Abnormal	3	2
Hyponatremia	2	1
Hypoproteinemia	5	3
SGOT Increased ^b	4	5
SGPT Increased ^b	5	5
Respiratory System		

Table 1. Incidence (%) of Adverse Reactions Through Test of Cure Reported in $\geq 2\%$ of Patients Treated in Clinical Studies

Body System	TYGACIL	Comparators^a
Adverse Reactions	(N=2514)	(N=2307)
Pneumonia	2	2
Nervous System		
Dizziness	3	3
Skin and Appendages		
Rash	3	4

^a Vancomycin/Aztreonam, Imipenem/Cilastatin, Levofloxacin, Linezolid.

^b LFT abnormalities in TYGACIL-treated patients were reported more frequently in the post therapy period than those in comparator-treated patients, which occurred more often on therapy.

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, an adjusted risk difference of all-cause mortality was 0.6% (95% CI 0.1, 1.2) between TYGACIL and comparator-treated patients (see Table 2). The cause of the imbalance has not been established. Generally, deaths were the result of worsening infection, complications of infection or underlying co-morbidities.

Table 2. Patients with Outcome of Death by Infection Type

Infection Type	TYGACIL		Comparator		Risk Difference* % (95% CI)
	n/N	%	n/N	%	
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 ^a	41/336	12.2	42/345	12.2	0.0 (-4.9, 4.9)
VAP ^a	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 Adjusted	150/3788	4.0	110/3646	3.0	0.6 (0.1, 1.2)**

CAP = Community-acquired pneumonia; cIAI = Complicated intra-abdominal infections; cSSSI = Complicated skin and skin structure infections; HAP = Hospital-acquired pneumonia; VAP = Ventilator-associated pneumonia; RP = Resistant pathogens; DFI = Diabetic foot infections.

* The difference between the percentage of patients who died in TYGACIL and comparator treatment groups. The 95% CI for each infection type was calculated using the normal approximation method without continuity correction.

** Overall adjusted (random effects model by trial weight) risk difference estimate and 95% CI.

^a These are subgroups of the HAP population.

Note: The studies include 300, 305, 900 (cSSSI), 301, 306, 315, 316, 400 (cIAI), 308 and 313 (CAP), 311 (HAP), 307 [Resistant gram-positive pathogen study in patients with MRSA or Vancomycin-Resistant Enterococcus (VRE)], and 319 (DFI with and without osteomyelitis).

An analysis of mortality in all trials conducted for approved indications - cSSSI, cIAI, and CAP, including post-market trials (315, 400, 900) - 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).

In comparative clinical studies, infection-related serious adverse events were more frequently reported for subjects treated with TYGACIL (7%) versus comparators (6%). Serious adverse events of sepsis/septic shock were more frequently reported for subjects treated with TYGACIL (2%) versus comparators (1%). Due to baseline differences between treatment groups in this subset of patients, the relationship of this outcome to treatment cannot be established [see *Warnings and Precautions* (5.9)].

The most common treatment-emergent adverse reactions were nausea and vomiting which generally occurred during the first 1 – 2 days of therapy. The majority of cases of nausea and vomiting associated with TYGACIL and comparators were either mild or moderate in severity. In patients treated with TYGACIL, nausea incidence was 26% (17% mild, 8% moderate, 1% severe) and vomiting incidence was 18% (11% mild, 6% moderate, 1% severe).

In patients treated for complicated skin and skin structure infections (cSSSI), nausea incidence was 35% for TYGACIL and 9% for vancomycin/aztreonam; vomiting incidence was 20% for

TYGACIL and 4% for vancomycin/aztreonam. In patients treated for complicated intra-abdominal infections (cIAI), nausea incidence was 25% for TYGACIL and 21% for imipenem/cilastatin; vomiting incidence was 20% for TYGACIL and 15% for imipenem/cilastatin. In patients treated for community-acquired bacterial pneumonia (CABP), nausea incidence was 24% for TYGACIL and 8% for levofloxacin; vomiting incidence was 16% for TYGACIL and 6% for levofloxacin.

Discontinuation from tigecycline was most frequently associated with nausea (1%) and vomiting (1%). For comparators, discontinuation was most frequently associated with nausea (<1%).

The following adverse reactions were reported infrequently (<2%) in patients receiving TYGACIL in clinical studies:

Body as a Whole: injection site inflammation, injection site pain, injection site reaction, septic shock, allergic reaction, chills, injection site edema, injection site phlebitis

Cardiovascular System: thrombophlebitis

Digestive System: anorexia, jaundice, abnormal stools

Metabolic/Nutritional System: increased creatinine, hypocalcemia, hypoglycemia

Special Senses: taste perversion

Hemic and Lymphatic System: partial thromboplastin time (aPTT), prolonged prothrombin time (PT), eosinophilia, increased international normalized ratio (INR), thrombocytopenia

Skin and Appendages: pruritus

Urogenital System: vaginal moniliasis, vaginitis, leukorrhea

6.2 Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of TYGACIL. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish causal relationship to drug exposure.

- anaphylaxis/anaphylactoid reactions
- acute pancreatitis
- hepatic cholestasis, and jaundice
- severe skin reactions, including Stevens-Johnson Syndrome
- symptomatic hypoglycemia in patients with and without diabetes mellitus

7 DRUG INTERACTIONS

7.1 Warfarin

Prothrombin time or other suitable anticoagulation test should be monitored if tigecycline is administered with warfarin [*see Clinical Pharmacology (12.3)*].

7.2 Oral Contraceptives

Concurrent use of antibacterial drugs with oral contraceptives may render oral contraceptives less effective.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects—Pregnancy Category D [*see Warnings and Precautions (5.6)*]

Tigecycline was not teratogenic in the rat or rabbit. In preclinical safety studies, ¹⁴C-labeled tigecycline crossed the placenta and was found in fetal tissues, including fetal bony structures. The administration of tigecycline was associated with reductions in fetal weights and an increased incidence of skeletal anomalies (delays in bone ossification) at exposures of 5 times and 1 times the human daily dose based on AUC in rats and rabbits, respectively (28 mcg·hr/mL and 6 mcg·hr/mL at 12 and 4 mg/kg/day). An increased incidence of fetal loss was observed at maternotoxic doses in the rabbits with exposure equivalent to human dose.

There are no adequate and well-controlled studies of tigecycline in pregnant women. TYGACIL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

Results from animal studies using ¹⁴C-labeled tigecycline indicate that tigecycline is excreted readily via the milk of lactating rats. Consistent with the limited oral bioavailability of tigecycline, there is little or no systemic exposure to tigecycline in nursing pups as a result of exposure via maternal milk.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TYGACIL is administered to a nursing woman [*see Warnings and Precautions (5.7)*].

8.4 Pediatric Use

Use in patients under 18 years of age is not recommended. Safety and effectiveness in pediatric patients below the age of 18 years have not been established. Because of the increased mortality observed in tigecycline-treated adult patients in clinical trials, pediatric trials of tigecycline to evaluate the safety and efficacy of tigecycline were not conducted.

In situations where there are no other alternative antibacterial drugs, pediatric dosing has been proposed based on data from pediatric pharmacokinetic studies [see *Dosage and Administration (2.3)* and *Clinical Pharmacology (12.3)*].

Because of effects on tooth development, use in patients under 8 years of age is not recommended [see *Warnings and Precautions (5.7)*].

8.5 Geriatric Use

Of the total number of subjects who received TYGACIL in Phase 3 clinical studies (n=2514), 664 were 65 and over, while 288 were 75 and over. No unexpected overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity to adverse events of some older individuals cannot be ruled out.

No significant difference in tigecycline exposure was observed between healthy elderly subjects and younger subjects following a single 100 mg dose of tigecycline [see *Clinical Pharmacology (12.3)*].

8.6 Hepatic Impairment

No dosage adjustment is warranted in patients with mild to moderate hepatic impairment (Child Pugh A and Child Pugh B). In patients with severe hepatic impairment (Child Pugh C), the initial dose of tigecycline should be 100 mg followed by a reduced maintenance dose of 25 mg every 12 hours. Patients with severe hepatic impairment (Child Pugh C) should be treated with caution and monitored for treatment response [see *Clinical Pharmacology (12.3)* and *Dosage and Administration (2.2)*].

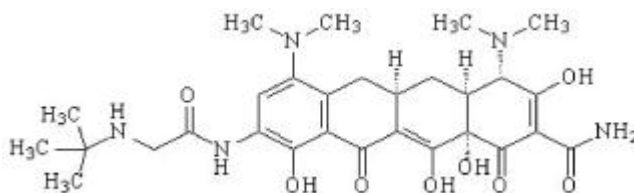
10 OVERDOSAGE

No specific information is available on the treatment of overdosage with tigecycline. Intravenous administration of TYGACIL at a single dose of 300 mg over 60 minutes in healthy volunteers resulted in an increased incidence of nausea and vomiting. In single-dose intravenous toxicity studies conducted with tigecycline in mice, the estimated median lethal dose (LD₅₀) was 124 mg/kg in males and 98 mg/kg in females. In rats, the estimated LD₅₀ was 106 mg/kg for both sexes. Tigecycline is not removed in significant quantities by hemodialysis.

11 DESCRIPTION

TYGACIL (tigecycline) is a tetracycline derivative (a glycylcycline) for intravenous infusion. The chemical name of tigecycline is (4*S*,4*aS*,5*aR*,12*aS*)-9-[2-(*tert*-butylamino)acetamido]-4,7-bis(dimethylamino)-1,4,4*a*,5,5*a*,6,11,12*a*-octahydro-3,10,12,12*a*-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide. The empirical formula is C₂₉H₃₉N₅O₈ and the molecular weight is 585.65.

The following represents the chemical structure of tigecycline:



TYGACIL is an orange lyophilized powder or cake. Each TYGACIL vial contains 50 mg tigecycline lyophilized powder for reconstitution for intravenous infusion and 100 mg of lactose monohydrate. The pH is adjusted with hydrochloric acid, and if necessary sodium hydroxide. The product does not contain preservatives.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tigecycline is an antibacterial drug [see *Clinical Pharmacology* (12.4)].

12.2 Pharmacodynamics

Cardiac Electrophysiology

No significant effect of a single intravenous dose of TYGACIL 50 mg or 200 mg on QTc interval was detected in a randomized, placebo- and active-controlled four-arm crossover thorough QTc study of 46 healthy subjects.

12.3 Pharmacokinetics

The mean pharmacokinetic parameters of tigecycline after single and multiple intravenous doses based on pooled data from clinical pharmacology studies are summarized in Table 3. Intravenous infusions of tigecycline were administered over approximately 30 to 60 minutes.

Table 3. Mean (CV%) Pharmacokinetic Parameters of Tigecycline

	Single Dose 100 mg (N=224)	Multiple Dose ^a 50 mg every 12h (N=103)
C _{max} (mcg/mL) ^b	1.45 (22%)	0.87 (27%)
C _{max} (mcg/mL) ^c	0.90 (30%)	0.63 (15%)
AUC (mcg·h/mL)	5.19 (36%)	- -
AUC _{0-24h} (mcg·h/mL)	- -	4.70 (36%)
C _{min} (mcg/mL)	- -	0.13 (59%)
t _{1/2} (h)	27.1 (53%)	42.4 (83%)
CL (L/h)	21.8 (40%)	23.8 (33%)
CL _r (mL/min)	38.0 (82%)	51.0 (58%)
V _{ss} (L)	568 (43%)	639 (48%)

^a 100 mg initially, followed by 50 mg every 12 hours

Table 3. Mean (CV%) Pharmacokinetic Parameters of Tigecycline

	Single Dose 100 mg (N=224)	Multiple Dose ^a 50 mg every 12h (N=103)
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^b 30-minute infusion^c 60-minute infusion

Distribution

The *in vitro* plasma protein binding of tigecycline ranges from approximately 71% to 89% at concentrations observed in clinical studies (0.1 to 1.0 mcg/mL). The steady-state volume of distribution of tigecycline averaged 500 to 700 L (7 to 9 L/kg), indicating tigecycline is extensively distributed beyond the plasma volume and into the tissues.

Following the administration of tigecycline 100 mg followed by 50 mg every 12 hours to 33 healthy volunteers, the tigecycline AUC_{0-12h} (134 mcg·h/mL) in alveolar cells was approximately 78-fold higher than the AUC_{0-12h} in the serum, and the AUC_{0-12h} (2.28 mcg·h/mL) in epithelial lining fluid was approximately 32% higher than the AUC_{0-12h} in serum. The AUC_{0-12h} (1.61 mcg·h/mL) of tigecycline in skin blister fluid was approximately 26% lower than the AUC_{0-12h} in the serum of 10 healthy subjects.

In a single-dose study, tigecycline 100 mg was administered to subjects prior to undergoing elective surgery or medical procedure for tissue extraction. Concentrations at 4 hours after tigecycline administration were higher in gallbladder (38-fold, n=6), lung (3.7-fold, n=5), and colon (2.3-fold, n=6), and lower in synovial fluid (0.58-fold, n=5), and bone (0.35-fold, n=6) relative to serum. The concentration of tigecycline in these tissues after multiple doses has not been studied.

Metabolism

Tigecycline is not extensively metabolized. *In vitro* studies with tigecycline using human liver microsomes, liver slices, and hepatocytes led to the formation of only trace amounts of metabolites. In healthy male volunteers receiving ¹⁴C-tigecycline, tigecycline was the primary ¹⁴C-labeled material recovered in urine and feces, but a glucuronide, an N-acetyl metabolite, and a tigecycline epimer (each at no more than 10% of the administered dose) were also present.

Elimination

The recovery of total radioactivity in feces and urine following administration of ¹⁴C-tigecycline indicates that 59% of the dose is eliminated by biliary/fecal excretion, and 33% is excreted in urine. Approximately 22% of the total dose is excreted as unchanged tigecycline in urine. Overall, the primary route of elimination for tigecycline is biliary excretion of unchanged tigecycline and its metabolites. Glucuronidation and renal excretion of unchanged tigecycline are secondary routes.

Specific Populations

Patients with Hepatic Impairment

In a study comparing 10 patients with mild hepatic impairment (Child Pugh A), 10 patients with moderate hepatic impairment (Child Pugh B), and 5 patients with severe hepatic impairment (Child Pugh C) to 23 age and weight matched healthy control subjects, the single-dose pharmacokinetic disposition of tigecycline was not altered in patients with mild hepatic impairment. However, systemic clearance of tigecycline was reduced by 25% and the half-life of tigecycline was prolonged by 23% in patients with moderate hepatic impairment (Child Pugh B). Systemic clearance of tigecycline was reduced by 55%, and the half-life of tigecycline was prolonged by 43% in patients with severe hepatic impairment (Child Pugh C). Dosage adjustment is necessary in patients with severe hepatic impairment (Child Pugh C) [see *Use in Specific Populations (8.6) and Dosage and Administration (2.2)*].

Patients with Renal Impairment

A single dose study compared 6 subjects with severe renal impairment (creatinine clearance <30 mL/min), 4 end stage renal disease (ESRD) patients receiving tigecycline 2 hours before hemodialysis, 4 ESRD patients receiving tigecycline 1 hour after hemodialysis, and 6 healthy control subjects. The pharmacokinetic profile of tigecycline was not significantly altered in any of the renally impaired patient groups, nor was tigecycline removed by hemodialysis. No dosage adjustment of TYGACIL is necessary in patients with renal impairment or in patients undergoing hemodialysis.

Geriatric Patients

No significant differences in pharmacokinetics were observed between healthy elderly subjects (n=15, age 65-75; n=13, age >75) and younger subjects (n=18) receiving a single 100-mg dose of TYGACIL. Therefore, no dosage adjustment is necessary based on age [see *Use in Specific Populations (8.5)*].

Pediatric Patients

A single-dose safety, tolerability, and pharmacokinetic study of tigecycline in pediatric patients aged 8-16 years who recently recovered from infections was conducted. The doses administered were 0.5, 1, or 2 mg/kg. The study showed that for children aged 12-16 years (n = 16) a dosage of 50 mg twice daily would likely result in exposures comparable to those observed in adults with the approved dosing regimen. Large variability observed in children aged 8 to 11 years of age (n = 8) required additional study to determine the appropriate dosage.

A subsequent tigecycline dose-finding study was conducted in 8-11 year old patients with cIAI, cSSSI, or CABP. The doses of tigecycline studied were 0.75 mg/kg (n = 17), 1 mg/kg (n = 21), and 1.25 mg/kg (n=20). This study showed that for children aged 8-11 years, a 1.2 mg/kg dose would likely result in exposures comparable to those observed in adults resulting with the approved dosing regimen [see *Dosage and Administration (2.3)*].

Gender

In a pooled analysis of 38 women and 298 men participating in clinical pharmacology studies, there was no significant difference in the mean ($\pm$ SD) tigecycline clearance between women (20.7 ± 6.5 L/h) and men (22.8 ± 8.7 L/h). Therefore, no dosage adjustment is necessary based on gender.

Race

In a pooled analysis of 73 Asian subjects, 53 Black subjects, 15 Hispanic subjects, 190 White subjects, and 3 subjects classified as “other” participating in clinical pharmacology studies, there was no significant difference in the mean ($\pm$ SD) tigecycline clearance among the Asian subjects (28.8 ± 8.8 L/h), Black subjects (23.0 ± 7.8 L/h), Hispanic subjects (24.3 ± 6.5 L/h), White subjects (22.1 ± 8.9 L/h), and “other” subjects (25.0 ± 4.8 L/h). Therefore, no dosage adjustment is necessary based on race.

Drug Interactions

TYGACIL (100 mg followed by 50 mg every 12 hours) and digoxin (0.5 mg followed by 0.25 mg, orally, every 24 hours) were co-administered to healthy subjects in a drug interaction study. Tigecycline slightly decreased the $C_{\max}$ of digoxin by 13%, but did not affect the AUC or clearance of digoxin. This small change in $C_{\max}$ did not affect the steady-state pharmacodynamic effects of digoxin as measured by changes in ECG intervals. In addition, digoxin did not affect the pharmacokinetic profile of tigecycline. Therefore, no dosage adjustment of either drug is necessary when TYGACIL is administered with digoxin.

Concomitant administration of TYGACIL (100 mg followed by 50 mg every 12 hours) and warfarin (25 mg single-dose) to healthy subjects resulted in a decrease in clearance of R-warfarin and S-warfarin by 40% and 23%, an increase in $C_{\max}$ by 38% and 43% and an increase in AUC by 68% and 29%, respectively. Tigecycline did not significantly alter the effects of warfarin on INR. In addition, warfarin did not affect the pharmacokinetic profile of tigecycline. However, prothrombin time or other suitable anticoagulation test should be monitored if tigecycline is administered with warfarin.

In vitro studies in human liver microsomes indicate that tigecycline does not inhibit metabolism mediated by any of the following 6 cytochrome P450 (CYP) isoforms: 1A2, 2C8, 2C9, 2C19, 2D6, and 3A4. Therefore, TYGACIL is not expected to alter the metabolism of drugs metabolized by these enzymes. In addition, because tigecycline is not extensively metabolized, clearance of tigecycline is not expected to be affected by drugs that inhibit or induce the activity of these CYP450 isoforms.

12.4 Microbiology

Mechanism of Action

Tigecycline, a glycylcycline, inhibits protein translation in bacteria by binding to the 30S ribosomal subunit and blocking entry of amino-acyl tRNA molecules into the A site of the ribosome. This prevents incorporation of amino acid residues into elongating peptide chains.

Tigecycline carries a glycyllamido moiety attached to the 9-position of minocycline. The substitution pattern is not present in any naturally occurring or semisynthetic tetracycline and imparts certain microbiologic properties to tigecycline. In general, tigecycline is considered bacteriostatic; however, TYGACIL has demonstrated bactericidal activity against isolates of *S. pneumoniae* and *L. pneumophila*.

Mechanism(s) of Resistance

To date there has been no cross-resistance observed between tigecycline and other antibacterials. Tigecycline is not affected by the two major tetracycline-resistance mechanisms, ribosomal protection and efflux. Additionally, tigecycline is not affected by resistance mechanisms such as beta-lactamases (including extended spectrum beta-lactamases), target-site modifications, macrolide efflux pumps or enzyme target changes (e.g. gyrase/topoisomerases). Tigecycline resistance in some bacteria (e.g. *Acinetobacter calcoaceticus*-*Acinetobacter baumannii* complex) is associated with multi-drug resistant (MDR) efflux pumps.

Interaction with Other Antimicrobials

In vitro studies have not demonstrated antagonism between tigecycline and other commonly used antibacterials.

Tigecycline has been shown to be active against most of the following bacteria, both *in vitro* and in clinical infections [see *Indications and Usage (1)*].

Facultative Gram-positive bacteria

Enterococcus faecalis (vancomycin-susceptible isolates)
Staphylococcus aureus (methicillin-susceptible and -resistant isolates)
Streptococcus agalactiae
Streptococcus anginosus grp. (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*)
Streptococcus pneumoniae (penicillin-susceptible isolates)
Streptococcus pyogenes

Facultative Gram-negative bacteria

Citrobacter freundii
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae (beta-lactamase negative isolates)
Klebsiella oxytoca
Klebsiella pneumoniae
Legionella pneumophila

Anaerobic bacteria

Bacteroides fragilis
Bacteroides thetaiotaomicron
Bacteroides uniformis

Bacteroides vulgatus
Clostridium perfringens
Peptostreptococcus micros

At least 90% of the following bacteria exhibit *in vitro* minimum inhibitory concentrations (MICs) that are at concentrations that are achievable using the prescribed dosing regimens. However, the clinical significance of this is unknown because the safety and effectiveness of tigecycline in treating clinical infections due to these bacteria have not been established in adequate and well-controlled clinical trials.

Facultative Gram-positive bacteria

Enterococcus avium
Enterococcus casseliflavus
Enterococcus faecalis (vancomycin-resistant isolates)
Enterococcus faecium (vancomycin-susceptible and -resistant isolates)
Enterococcus gallinarum
Listeria monocytogenes
Staphylococcus epidermidis (methicillin-susceptible and -resistant isolates)
Staphylococcus haemolyticus

Facultative Gram-negative bacteria

*Acinetobacter baumannii**
Aeromonas hydrophila
Citrobacter koseri
Enterobacter aerogenes
Haemophilus influenzae (ampicillin-resistant)
Haemophilus parainfluenzae
Pasteurella multocida
Serratia marcescens
Stenotrophomonas maltophilia

Anaerobic bacteria

Bacteroides distasonis
Bacteroides ovatus
Peptostreptococcus spp.
Porphyromonas spp.
Prevotella spp.

Other bacteria

Mycobacterium abscessus
Mycobacterium fortuitum

*There have been reports of the development of tigecycline resistance in *Acinetobacter* infections seen during the course of standard treatment. Such resistance appears to be attributable

to an MDR efflux pump mechanism. While monitoring for relapse of infection is important for all infected patients, more frequent monitoring in this case is suggested. If relapse is suspected, blood and other specimens should be obtained and cultured for the presence of bacteria. All bacterial isolates should be identified and tested for susceptibility to tigecycline and other appropriate antimicrobials.

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide cumulative results of the *in vitro* susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure based on dilution methods (broth, agar, or microdilution)^{1,3,4} or equivalent using standardized inoculum and concentrations of tigecycline. For broth dilution tests for aerobic organisms, MICs must be determined in testing medium that is fresh (<12h old). The MIC values should be interpreted according to the criteria provided in Table 4.

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The standardized procedure^{2,4} requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 15 mcg tigecycline to test the susceptibility of bacteria to tigecycline. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for tigecycline. Reports from the laboratory providing results of the standard single-disk susceptibility test with a 15 mcg tigecycline disk should be interpreted according to the criteria in Table 4.

Anaerobic Techniques

Anaerobic susceptibility testing with tigecycline should be done by the agar dilution method³ since quality control parameters for broth-dilution are not established.

Table 4. Susceptibility Test Result Interpretive Criteria for Tigecycline

Pathogen	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameters in mm)		
	S	I	R	S	I	R
<i>Staphylococcus aureus</i> (including methicillin-resistant isolates)	≤0.5 ^a	-	-	≥19	-	-

Table 4. Susceptibility Test Result Interpretive Criteria for Tigecycline

Pathogen	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameters in mm)		
	S	I	R	S	I	R
<i>Streptococcus</i> spp. other than <i>S. pneumoniae</i>	≤0.25 ^a	-	-	≥19	-	-
<i>Streptococcus pneumoniae</i>	≤0.06 ^a	-	-	≥19	-	-
<i>Enterococcus faecalis</i> (vancomycin-susceptible isolates)	≤0.25 ^a	-	-	≥19	-	-
Enterobacteriaceae ^b	≤2	4	≥8	≥19	15-18	≤14
<i>Haemophilus influenzae</i>	≤0.25 ^a	-	-	≥19	-	-
Anaerobes ^c	≤4	8	≥16	n/a	n/a	n/a

^a The current absence of resistant isolates precludes defining any results other than “Susceptible.” Isolates yielding MIC results suggestive of “Nonsusceptible” category should be submitted to reference laboratory for further testing.

^b Tigecycline has decreased *in vitro* activity against *Morganella* spp., *Proteus* spp. and *Providencia* spp.

^c Agar dilution

A report of “Susceptible” indicates that the pathogen is likely to be inhibited if the antimicrobial compound reaches the concentrations usually achievable. A report of “Intermediate” indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of “Resistant” indicates that the pathogen is not likely to be inhibited if the antimicrobial compound reaches the concentrations usually achievable; other therapy should be selected.

Quality Control

As with other susceptibility techniques, the use of laboratory control microorganisms is required to control the technical aspects of the laboratory standardized procedures.^{1,2,3,4} Standard tigecycline powder should provide the MIC values provided in Table 5. For the diffusion technique using the 15 mcg tigecycline disk the criteria provided in Table 5 should be achieved.

Table 5. Acceptable Quality Control Ranges for Susceptibility Testing

QC organism	Minimum Inhibitory Concentrations (mcg/mL)	Disk Diffusion (zone diameters in mm)
<i>Staphylococcus aureus</i> ATCC 25923	Not Applicable	20-25
<i>Staphylococcus aureus</i> ATCC 29213	0.03-0.25	Not Applicable

Table 5. Acceptable Quality Control Ranges for Susceptibility Testing

QC organism	Minimum Inhibitory Concentrations (mcg/mL)	Disk Diffusion (zone diameters in mm)
<i>Escherichia coli</i> ATCC 25922	0.03-0.25	20-27
<i>Enterococcus faecalis</i> ATCC 29212	0.03-0.12	Not Applicable
<i>Streptococcus pneumoniae</i> ATCC 49619	0.016-0.12	23-29
<i>Haemophilus influenzae</i> ATCC 49247	0.06-0.5	23-31
<i>Bacteroides fragilis</i> ^a ATCC 25285	0.12-1	Not Applicable
<i>Bacteroides thetaiotaomicron</i> ^a ATCC 29741	0.5-2	Not Applicable
<i>Eubacterium lentum</i> ^a ATCC 43055	0.06-0.5	Not Applicable
<i>Clostridium difficile</i> ^a ATCC 70057	0.12-1	Not Applicable

ATCC = American Type Culture Collection

^a Agar dilution

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Lifetime studies in animals have not been performed to evaluate the carcinogenic potential of tigecycline. No mutagenic or clastogenic potential was found in a battery of tests, including *in vitro* chromosome aberration assay in Chinese hamster ovary (CHO) cells, *in vitro* forward mutation assay in CHO cells (HGRPT locus), *in vitro* forward mutation assays in mouse lymphoma cells, and *in vivo* mouse micronucleus assay. Tigecycline did not affect mating or fertility in rats at exposures up to 5 times the human daily dose based on AUC (28 mcg·hr/mL at 12 mg/kg/day). In female rats, there were no compound-related effects on ovaries or estrous cycles at exposures up to 5 times the human daily dose based on AUC.

13.2 Animal Toxicology and/or Pharmacology

In two week studies, decreased erythrocytes, reticulocytes, leukocytes, and platelets, in association with bone marrow hypocellularity, have been seen with tigecycline at exposures of 8 times and 10 times the human daily dose based on AUC in rats and dogs, (AUC of approximately 50 and 60 mcg·hr/mL at doses of 30 and 12 mg/kg/day) respectively. These alterations were shown to be reversible after two weeks of dosing.

14 CLINICAL STUDIES

14.1 Complicated Skin and Skin Structure Infections

TYGACIL was evaluated in adults for the treatment of complicated skin and skin structure infections (cSSSI) in two randomized, double-blind, active-controlled, multinational, multicenter studies (Studies 300 and 305). These studies compared TYGACIL (100 mg intravenous initial dose followed by 50 mg every 12 hours) with vancomycin (1 g intravenous every 12 hours)/aztreonam (2 g intravenous every 12 hours) for 5 to 14 days. Patients with complicated deep soft tissue infections including wound infections and cellulitis (≥ 10 cm, requiring surgery/drainage or with complicated underlying disease), major abscesses, infected ulcers, and burns were enrolled in the studies. The primary efficacy endpoint was the clinical response at the test of cure (TOC) visit in the co-primary populations of the clinically evaluable (CE) and clinical modified intent-to-treat (c-mITT) patients. See Table 6. Clinical cure rates at TOC by pathogen in the microbiologically evaluable patients are presented in Table 7.

Table 6. Clinical Cure Rates from Two Studies in Complicated Skin and Skin Structure Infections after 5 to 14 Days of Therapy

	TYGACIL ^a n/N (%)	Vancomycin/Aztreonam ^b n/N (%)
Study 300		
CE	165/199 (82.9)	163/198 (82.3)
c-mITT	209/277 (75.5)	200/260 (76.9)
Study 305		
CE	200/223 (89.7)	201/213 (94.4)
c-mITT	220/261 (84.3)	225/259 (86.9)

^a 100 mg initially, followed by 50 mg every 12 hours

^b Vancomycin (1 g every 12 hours)/Aztreonam (2 g every 12 hours)

Table 7. Clinical Cure Rates By Infecting Pathogen in Microbiologically Evaluable Patients with Complicated Skin and Skin Structure Infections^a

Pathogen	TYGACIL n/N (%)	Vancomycin/Aztreonam n/N (%)
<i>Escherichia coli</i>	29/36 (80.6)	26/30 (86.7)
<i>Enterobacter cloacae</i>	10/12 (83.3)	15/15 (100)
<i>Enterococcus faecalis</i> (vancomycin-susceptible only)	15/21 (71.4)	19/24 (79.2)
<i>Klebsiella pneumoniae</i>	12/14 (85.7)	15/16 (93.8)
Methicillin-susceptible <i>Staphylococcus aureus</i> (MSSA)	124/137 (90.5)	113/120 (94.2)
Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)	79/95 (83.2)	46/57 (80.7)
<i>Streptococcus agalactiae</i>	8/8 (100)	11/14 (78.6)
<i>Streptococcus anginosus</i> grp. ^b	17/21 (81.0)	9/10 (90.0)
<i>Streptococcus pyogenes</i>	31/32 (96.9)	24/27 (88.9)
<i>Bacteroides fragilis</i>	7/9 (77.8)	4/5 (80.0)

^a Two cSSSI pivotal studies and two Resistant Pathogen studies

^b Includes *Streptococcus anginosus*, *Streptococcus intermedius*, and *Streptococcus constellatus*

14.2 Complicated Intra-abdominal Infections

TYGACIL was evaluated in adults for the treatment of complicated intra-abdominal infections (cIAI) in two randomized, double-blind, active-controlled, multinational, multicenter studies (Studies 301 and 306). These studies compared TYGACIL (100 mg intravenous initial dose followed by 50 mg every 12 hours) with imipenem/cilastatin (500 mg intravenous every 6 hours) for 5 to 14 days. Patients with complicated diagnoses including appendicitis, cholecystitis, diverticulitis, gastric/duodenal perforation, intra-abdominal abscess, perforation of intestine, and peritonitis were enrolled in the studies. The primary efficacy endpoint was the clinical response at the TOC visit for the co-primary populations of the microbiologically evaluable (ME) and the microbiologic modified intent-to-treat (m-mITT) patients. See Table 8. Clinical cure rates at TOC by pathogen in the microbiologically evaluable patients are presented in Table 9.

Table 8. Clinical Cure Rates from Two Studies in Complicated Intra-abdominal Infections after 5 to 14 Days of Therapy

	TYGACIL ^a n/N (%)	Imipenem/Cilastatin ^b n/N (%)
Study 301		
ME	199/247 (80.6)	210/255 (82.4)
m-mITT	227/309 (73.5)	244/312 (78.2)
Study 306		
ME	242/265 (91.3)	232/258 (89.9)
m-mITT	279/322 (86.6)	270/319 (84.6)

^a 100 mg initially, followed by 50 mg every 12 hours

^b Imipenem/Cilastatin (500 mg every 6 hours)

Table 9. Clinical Cure Rates By Infecting Pathogen in Microbiologically Evaluable Patients with Complicated Intra-abdominal Infections^a

Pathogen	TYGACIL n/N (%)	Imipenem/Cilastatin n/N (%)
<i>Citrobacter freundii</i>	12/16 (75.0)	3/4 (75.0)
<i>Enterobacter cloacae</i>	15/17 (88.2)	16/17 (94.1)
<i>Escherichia coli</i>	284/336 (84.5)	297/342 (86.8)
<i>Klebsiella oxytoca</i>	19/20 (95.0)	17/19 (89.5)
<i>Klebsiella pneumoniae</i>	42/47 (89.4)	46/53 (86.8)
<i>Enterococcus faecalis</i>	29/38 (76.3)	35/47 (74.5)
Methicillin-susceptible <i>Staphylococcus aureus</i> (MSSA)	26/28 (92.9)	22/24 (91.7)
Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)	16/18 (88.9)	1/3 (33.3)
<i>Streptococcus anginosus</i> grp. ^b	101/119 (84.9)	60/79 (75.9)
<i>Bacteroides fragilis</i>	68/88 (77.3)	59/73 (80.8)
<i>Bacteroides thetaiotaomicron</i>	36/41 (87.8)	31/36 (86.1)
<i>Bacteroides uniformis</i>	12/17 (70.6)	14/16 (87.5)
<i>Bacteroides vulgatus</i>	14/16 (87.5)	4/6 (66.7)
<i>Clostridium perfringens</i>	18/19 (94.7)	20/22 (90.9)
<i>Peptostreptococcus micros</i>	13/17 (76.5)	8/11 (72.7)

^a Two cIAI pivotal studies and two Resistant Pathogen studies

^b Includes *Streptococcus anginosus*, *Streptococcus intermedius*, and *Streptococcus constellatus*

14.3 Community-Acquired Bacterial Pneumonia

TYGACIL was evaluated in adults for the treatment of community-acquired bacterial pneumonia (CABP) in two randomized, double-blind, active-controlled, multinational, multicenter studies (Studies 308 and 313). These studies compared TYGACIL (100 mg intravenous initial dose followed by 50 mg every 12 hours) with levofloxacin (500 mg intravenous every 12 or 24

hours). In one study (Study 308), after at least 3 days of intravenous therapy, a switch to oral levofloxacin (500 mg daily) was permitted for both treatment arms. Total therapy was 7 to 14 days. Patients with community-acquired bacterial pneumonia who required hospitalization and intravenous therapy were enrolled in the studies. The primary efficacy endpoint was the clinical response at the test of cure (TOC) visit in the co-primary populations of the clinically evaluable (CE) and clinical modified intent-to-treat (c-mITT) patients. See Table 10. Clinical cure rates at TOC by pathogen in the microbiologically evaluable patients are presented in Table 11.

Table 10. Clinical Cure Rates from Two Studies in Community-Acquired Bacterial Pneumonia after 7 to 14 Days of Total Therapy

	TYGACIL ^a n/N (%)	Levofloxacin ^b n/N (%)	95% CI ^c
Study 308 ^d			
CE	125/138 (90.6)	136/156 (87.2)	(-4.4, 11.2)
c-mITT	149/191 (78)	158/203 (77.8)	(-8.5, 8.9)
Study 313			
CE	128/144 (88.9)	116/136 (85.3)	(-5.0, 12.2)
c-mITT	170/203 (83.7)	163/200 (81.5)	(-5.6, 10.1)

^a 100 mg initially, followed by 50 mg every 12 hours

^b Levofloxacin (500 mg intravenous every 12 or 24 hours)

^c 95% confidence interval for the treatment difference

^d After at least 3 days of intravenous therapy, a switch to oral levofloxacin (500 mg daily) was permitted for both treatment arms in Study 308.

Table 11. Clinical Cure Rates By Infecting Pathogen in Microbiologically Evaluable Patients with Community-Acquired Bacterial Pneumonia^a

Pathogen	TYGACIL n/N (%)	Levofloxacin n/N (%)
<i>Haemophilus influenzae</i>	14/17 (82.4)	13/16 (81.3)
<i>Legionella pneumophila</i>	10/10 (100.0)	6/6 (100.0)
<i>Streptococcus pneumoniae</i> (penicillin-susceptible only) ^b	44/46 (95.7)	39/44 (88.6)

^a Two CABP studies

^b Includes cases of concurrent bacteremia [cure rates of 20/22 (90.9%) versus 13/18 (72.2%) for TYGACIL and levofloxacin respectively]

To further evaluate the treatment effect of tigecycline, a post-hoc analysis was conducted in CABP patients with a higher risk of mortality, for whom the treatment effect of antibiotics is supported by historical evidence. The higher-risk group included CABP patients from the two studies with any of the following factors:

- Age ≥ 50 years
- PSI score ≥ 3
- *Streptococcus pneumoniae* bacteremia

The results of this analysis are shown in Table 12. Age ≥ 50 was the most common risk factor in the higher-risk group.

Table 12. Post-hoc Analysis of Clinical Cure Rates in Patients with Community-Acquired Bacterial Pneumonia Based on Risk of Mortality^a

	TYGACIL n/N (%)	Levofloxacin n/N (%)	95% CI ^b
Study 308 ^c			
CE			
Higher risk			
Yes	93/103 (90.3)	84/102 (82.4)	(-2.3, 18.2)
No	32/35 (91.4)	52/54 (96.3)	(-20.8, 7.1)
c-mITT			
Higher risk			
Yes	111/142 (78.2)	100/134 (74.6)	(-6.9, 14)
No	38/49 (77.6)	58/69 (84.1)	(-22.8, 8.7)
Study 313			
CE			
Higher risk			
Yes	95/107 (88.8)	68/85 (80)	(-2.2, 20.3)
No	33/37 (89.2)	48/51 (94.1)	(-21.1, 8.6)
c-mITT			
Higher risk			
Yes	112/134 (83.6)	93/120 (77.5)	(-4.2, 16.4)
No	58/69 (84.1)	70/80 (87.5)	(-16.2, 8.8)

^a Patients at higher risk of death include patients with any one of the following: ≥ 50 year of age; PSI score ≥ 3 ; or bacteremia due to *Streptococcus pneumoniae*

^b 95% confidence interval for the treatment difference

^c After at least 3 days of intravenous therapy, a switch to oral levofloxacin (500 mg daily) was permitted for both treatment arms in Study 308.

15 REFERENCES

1. Clinical and Laboratory Standards Institute (CLSI). *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard - Ninth Edition*. CLSI document M07-A9, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2012.

2. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Disk Diffusion Susceptibility Tests; Approved Standard – Eleventh Edition*. CLSI document M02-A11, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2012.
3. Clinical and Laboratory Standards Institute (CLSI). *Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria; Approved Standard - Eight Edition*. CLSI document M11-A8. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, PA 19087 USA, 2012.
4. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-third Informational Supplement*. CLSI document M100-S23. CLSI document M100-S23, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2013.

16 HOW SUPPLIED/STORAGE AND HANDLING

TYGACIL (tigecycline) for injection is supplied in a single-dose 5 mL glass vial or 10 mL glass vial, each containing 50 mg tigecycline lyophilized powder for reconstitution.

Supplied:

5 mL - 10 vials/box. NDC 0008-4990-02

10 mL - 10 vials/box. NDC 0008-4990-20

Prior to reconstitution, TYGACIL should be stored at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature.] Once reconstituted, TYGACIL may be stored at room temperature (not to exceed 25°C/77°F) for up to 24 hours (up to 6 hours in the vial and the remaining time in the intravenous bag). If the storage conditions exceed 25°C (77°F) after reconstitution, tigecycline should be used immediately. Alternatively, TYGACIL mixed with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP may be stored refrigerated at 2° to 8°C (36° to 46°F) for up to 48 hours following immediate transfer of the reconstituted solution into the intravenous bag. Reconstituted solution must be transferred and further diluted for intravenous infusion.

17 PATIENT COUNSELING INFORMATION

- Patients should be counseled that antibacterial drugs including TYGACIL should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When TYGACIL is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by TYGACIL or other antibacterial drugs in the future.

- Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.



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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-821/S026/S031

MEDICAL REVIEW(S)

Clinical Review Addendum
NDA 21-821 Labeling Supplements SLR-026 and SLR-031

Drug Product: Tygacil® (Tigecycline) for Injection

Date of Submission: September 23, 2013

Applicant: Pfizer, Inc.

Summary:

This submission contains the agreed-upon labeling text as described in the Medical Officer reviews dated July 23, and August 7, 2013. One change from the proposed labeling described in these reviews was requested by the Agency. The following statement in the Boxed Warning and Warnings and Precautions, 5.1 All-Cause Mortality section:

“This increase in all-cause mortality should be considered when selecting among treatment options”

was changed to:

“TYGACIL should be reserved for situations when alternative treatments are not suitable”

The applicant accepted the proposed labeling.

Conclusions:

The submission contains the agreed-upon labeling. The labeling supplements for tigecycline can be approved.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOHN J ALEXANDER
09/25/2013

Medical Officer Review of Tigecycline Labeling Supplements and a Final Report of a Phase 3 Trial of Tigecycline for the Treatment of Diabetic Foot Infection (DFI)

NDA 21,821

Drug Product: TYGACIL™ (tigecycline)

Applicant: Wyeth Pharmaceuticals
500 Arcola Road
Collegeville, PA 19426

Reviewed Submissions:

- Prior Approval Supplement (PAS)-026 including a final report of the DFI trial submitted on September 29, 2009, amended on November 29, 2011 and on July 03, 2013.
- Changes Being Effectuated (CBE-0) supplement-031 submitted on February 11, 2011 and amended on July 03, 2013.

Reviewer: Dmitri Iarikov, Division of Anti-Infective Products

Review Completed: July 23, 2013

Reviewed Documents:

1. Tigecycline labeling supplements
2. Final report of a multicenter, randomized, double blind comparison of the safety and efficacy of a once-daily dose of tigecycline versus ertapenem for the treatment of foot infections in subjects with diabetes.
3. Justification for a safety labeling decision for tigecycline - Stevens - Johnson syndrome, 23 August 2010
4. Justification for a safety labeling decision for tigecycline - Hypoglycemia, (b) (4) Pneumonia, USPI ADR Frequency Modifications, 24 January 2011

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2 Executive Summary

This review includes two labeling supplements and subsequent amendments. During the review of these supplements, a citizen petition requesting several changes to the tigecycline label was submitted on October 28, 2011 by Public Citizen, a national, nonprofit consumer advocacy organization. The review and responses to the petition resulted in putting on hold the actions on the labeling supplements. As a result, the label under this review combines supplements and subsequent amendments submitted from September 2009 to July 2013. The supplement and amendments are mainly related to safety concerns and include, along with other changes, a boxed warning informing about increased mortality associated with tigecycline use.

The prior approval supplement (PAS) submission from September 29, 2009 revises the "Indications and Usage" and "Clinical Studies" sections of the physician's package with information that TYGACIL is not indicated for the treatment of diabetic foot infections. The submission also includes a final report of a multicenter, randomized, double-blind, comparison study of the safety and efficacy of a once-daily dose of tigecycline versus ertapenem for the treatment of foot infections in subjects with diabetes (Protocol 3074K5-319-WW).

The changes being effected supplement (CBE) submission from February 11, 2011 provides for changes to the "Adverse Reactions" section of the labeling. Specifically, the adverse events of pneumonia and severe skin reactions, including Stevens-Johnson syndrome have been added. In addition, a number of discrepancies between adverse reaction (ADR) frequencies observed in the clinical database and those reported in the Tygacil USPI have been corrected. Modifications made to the ADR frequencies for Abscess, Infection, Anemia, Alkaline Phosphatase and Healing Abnormal in Table 1 of the label reporting adverse reactions occurring in $\geq 2\%$ of patients. Hyponatremia was moved from the $\leq 2\%$ section to Table 1.

The Sponsor explain the basis for these modifications in a document titled "Justification for a safety labeling decision for tigecycline - Hypoglycemia, (b) (4) Pneumonia, USPI ADR Frequency Modifications" dated 24 January 2011. The review of this supporting documents is also included.

The most recent amendments to both supplements were submitted on July 03, 2013. These amendments include a boxed warning informing about an increase in mortality associated with the use of tigecycline. This recommendation is based on additional analyses of safety information collected in tigecycline trials that have been conducted by the FDA suggesting that an increase in mortality may be present not only in non-approved but also in approved tigecycline indications. The label also incorporates amendments to Indications and Usage, Warning and Precautions, and Adverse Reactions sections. The label with track changes is included as Attachment 1 in this review.

3 Review of a Prior Approval supplement submitted on September 30, 2009

3.1 Indications and Usage, Limitations of Use

The reason for changes in the labeling proposed in the Prior Approval Supplement submitted on 9/29/2009 is the failure of tigecycline to demonstrate non-inferiority in a randomized, double blind trial which compared the safety and efficacy of tigecycline versus ertapenem for the treatment of diabetic foot infections (Study 319). The trial evaluated the efficacy of tigecycline in subjects with diabetic foot infections without osteomyelitis (primary study), and with osteomyelitis (osteomyelitis substudy).

The Sponsor suggested adding a sentence that TYGACIL is not indicated for the treatment of diabetic foot infections (b) (4) in the Indications and Usage section. The Sponsor also suggested (b) (4)

Medical Officer (MO) comments: The Division believed, however, that the information that TYGACIL is not indicated for the treatment of diabetic foot infection (DFI) (b) (4) (b) (4) Diabetic foot infection represents a distinct indication and was studied in a separate trial. The Indications and Usage section should be added with a subsection titled Limitations of Use informing that tigecycline failed to demonstrate effectiveness in diabetic foot infections. In addition, the section should also include information that tigecycline failed to demonstrate effectiveness in hospital acquired pneumonia. The added language is as follows:

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 and Precautions (5.2)].

The MO suggests (b) (4) This section describes studies where the drug demonstrated safety and effectiveness supporting its approval for respective indications. (b) (4) The reader is referred to Attachment 1 to see the proposed text of the respective labeling sections. (b) (4)

4 Review of a Changes Being Effected Labeling Supplement submitted on February 11, 2011

4.1 Post-Marketing Experience, section 6.2

Severe skin reactions, including Stevens - Johnson syndrome and hypoglycemia have been added to the section.

A total of seven reports of Stevens-Johnson syndrome were identified by the Sponsor by searching the pharmacovigilance database for tigecycline adverse events reports received through 14 June 2010 and containing Preferred Terms within the Bullous conditions MedDRA High Level Term (HLT). Four of these reports contained minimal information with regard to medical history, concomitant medications, clinical course, and outcome. The association between Stevens-Johnson syndrome and tigecycline can not be ruled out in three reports. The section 6.2 Post-Marketing Experience of the label is revised to include severe skin reactions, including Stevens-Johnson syndrome.

MO comments: The inclusion of adding Steven-Johnson syndrome to section 6.2 of the label is acceptable. The reader is referred to Attachment 1 to see the proposed text of the respective labeling sections.

Further review of supporting documents provided by the Sponsor and explaining changes made to the Tigecycline Core Data sheet resulted in the Division's recommendation to include hypoglycemia in subsection 6.2 Post-Marketing Experience, see Review of Supporting Documents for Safety Labeling Decisions (CDS) section of this review. The section is suggested to reads as follows:

6.2 Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of TYGACIL. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish causal relationship to drug exposure.

- anaphylaxis/anaphylactoid reactions
- acute pancreatitis
- hepatic cholestasis, and jaundice
- severe skin reactions, including Stevens-Johnson Syndrome
- symptomatic hypoglycemia in patients with and without diabetes mellitus

Table 1 in Section 6-ADVERSE REACTIONS has been revised with new frequencies for some terms to make the USPI consistent with the information contained within the current Tygacil clinical study database. In addition, the term pneumonia has been added and the term (b) (4) has moved from (b) (4) to Table 1.

Table 1: Incidence (%) of Adverse Reactions Through Test of Cure Reported in $\geq 2\%$ of

Patients Treated in Clinical Studies - only revised incidence is presented

Body System Adverse reactions	TYGACYL (N=2514)	Comparators (N=2307)
Body as a Whole		
Abscess	2 (b) (4)	2 (b) (4)
Infection	7	5
Hemic and Lymphatic System		
Anemia	5	6
Metabolic and Nutritional		
Alkaline Phosphatase	3	3
Healing Abnormal	3	2
Hyponatremia	2	1
Respiratory System		
Pneumonia	2	2

MO comments: The changes to Table 1 in section 6 of the label seem acceptable. During the review we requested the number (%) of tigecycline patients and the number (%) of comparator patients from each study included in the table with the following AE: Abscess, Infection, Alkaline Phosphatase Increased, Anemia, and Hyponatremia, Pneumonia and Abnormal healing. The Sponsor provided the requested information and the changes in the label are found to be acceptable.

5 Review of Labeling Amendments submitted on July 03, 2013

5.1 Boxed Warning and Warning and Precautions Sections

In randomized clinical trials of tigecycline, more deaths were noted in the tigecycline arm in the initial cSSSI and cIAI tigecycline trials as well as in the majority of subsequent trials of cIAI, hospital-acquired pneumonia (HAP), CABP, resistant pathogens (RP), and DFI (tigecycline trials by infection types and observed mortality are listed in Table 2 of this review). An increase over active control in all-cause mortality risk of approximately 1% among tigecycline-treated patients was noted when the results of all trials were combined. Although for each indication, the mortality difference was not statistically significant, mortality in tigecycline-treated patients was numerically greater in every infection, and was particularly greater in VAP, a subgroup of HAP. As mentioned above, Tygacil is not approved for HAP because of an unacceptably low cure rate relative to active-control as well as excess mortality.

Several investigations of tigecycline-associated mortality have been conducted by FDA. Thus, a meta-analysis of all thirteen comparative trials estimated the mortality risk in tigecycline and comparator treated patients, Table 2. Another meta-analysis of eight selected trials that had similar design, patient populations and available patient-level data assessed the relationship between tigecycline and mortality using patient-level variables including demographic information, baseline laboratory test results, baseline pathogens, and medical history.

Table 2: Patients with outcome of death by infection type			
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)
clAI	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; clAI = 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			

In addition, including a retrospective case review of all reported deaths in fourteen pre- and post-approval tigecycline trials was conducted. The primary objective of the case review was to assess for an association between the increase in mortality and a possible lack of efficacy and/or increased toxicity of tigecycline or comparators among all reported deaths. The secondary objectives included assessing for an association between mortality risk and baseline comorbidities, specific adverse events during study, and causative pathogens of the underlying infection.

These meta-analyses and the case review of deaths did not identify tigecycline-related toxicities, specific patient-level characteristics or other risk factors driving this mortality imbalance. The case review of deaths in tigecycline trials analyses suggests that the increase mortality in tigecycline treated patients was deaths were related to the progression of underlying diseases and infections. A pooled analysis of 13 trials conducted by FDA demonstrated a higher mortality with tigecycline relative to comparators, adjusted risk difference of 0.6% and 95% confidence interval (0.1, 1.2), Table 2. The difference in mortality was mainly driven by patients with VAP, an unapproved use.

These meta-analyses and the case review FDA analyses resulted in updates to the Warning and Precautions and Adverse Reactions sections of the product label with the most recent update in July of 2010 and an FDA Safety Communication in September of 2010 titled “Increased risk of death with Tygacil (tigecycline) compared to other antibacterial drugs used to treat similar infections” . Healthcare professionals have also been informed of this increased risk via a Dear Health Care Professional letter issued by the Sponsor in July, 2010.

After the publication of the Safety communication, the FDA has conducted additional analyses of safety information collected in tigecycline clinical trials. An analysis of

mortality in all trials conducted for approved indications - cSSSI, cIAI, and CABP, including post-market trials (315 (b) (4) 400, 900) demonstrated the mortality rate (b) (4). The adjusted risk difference for mortality stratified by trial weight was 0.6% (95% CI 0.0, 1.2). Therefore, these analyses suggest that an increase risk in tigecycline-associated mortality may be present not only in non-approved but also in approved tigecycline indications.

As a result, it was deemed necessary to present the information about an increase in mortality as a boxed warning. The Warning and precautions section has also been revised. The Boxed Warning the Warnings and Precautions section in the revised tigecycline labeling reads as follows:

WARNING:

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.

(b) (4)
Warnings and Precautions (5.1, 5.2) and Adverse Reactions (6.1)].

5 WARNINGS AND PRECAUTIONS

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.

(b) (4)
Warnings and Precautions (5.2) and Adverse Reactions (6.1)].

5.2 Clinical Trials Experience

The results of analyses of mortality in trials for approved indications are included in the revised tigecycline labeling, subsection 6.1 Clinical Trials Experience:

An analysis of mortality in all trials conducted for approved indications - cSSSI, cIAI, and CABP, including post-market trials (315 (b) (4), 400, 900) demonstrated the mortality rate (b) (4). The adjusted risk difference for mortality stratified by trial weight was 0.6% (95% CI 0.0, 1.2).

5.3 Dosage and Administration, Pediatric Patients, subsection 2.3

Since conducting pediatric trials evaluating efficacy and safety of tigecycline was deemed to be inappropriate because of increased mortality observed in adults, a waiver to conduct pediatric studies was granted. After discussion with the members of Pediatric Review Committee, the following text was decided to be included in the label:

2.3 Pediatric Patients

The safety and efficacy of the proposed pediatric dosing regimens have not been evaluated due to the observed increase in mortality associated with tigecycline in adult patients. Tigecycline should not be used in pediatric patients unless no alternative antibacterial drugs are available. Under these circumstances, the following doses are suggested:

- Pediatric patients aged 8 to 11 years should receive 1.2 mg/kg of tigecycline every 12 hours intravenously to a maximum dose of 50 mg of tigecycline every 12 hours.
- Pediatric patients aged 12 to 17 years should receive 50 mg of tigecycline every 12 hours,

The proposed pediatric doses of tigecycline were chosen based on exposures observed in pharmacokinetic trials, which included small numbers of pediatric patients [see *Use in Specific Populations (8.4) and Clinical Pharmacology (12.3)*].

5.4 Pediatric Use, subsection 8.4

Because of the increased mortality observed in tigecycline-treated adult patients, pediatric trials to evaluate the safety and efficacy of tigecycline were not conducted. The subsection 8.4 Pediatric Use was amended as follows:

Use in patients under 18 years of age is not recommended. Safety and effectiveness in pediatric patients below the age of 18 years have not been established. Because of the increased mortality observed in tigecycline-treated adult patients in clinical trials, pediatric trials of tigecycline to evaluate the safety and efficacy of tigecycline were not conducted.

In situations where there are no other alternative antibacterial drugs, pediatric dosing has been proposed based on data from pediatric pharmacokinetic studies [see *Dosage and Administration (2.3) and Clinical Pharmacology (12.3)*].

5.5 Cardiac Electrophysiology

At the time of approval of Tygacil in June 2005, a thorough QT study had not been performed. After the approval, higher overall mortality had been observed in accumulating data from phase 3 and phase 4 clinical trials including a higher number of

deaths related to cardiovascular events occurring in the tigecycline group. Also, in some trials, QT prolongation was seen more frequently in tigecycline-treated patients.

Therefore, the question whether Tygacil causes QT prolongation needed to be addressed in order to evaluate the possibility of torsades de pointes as a cause of death in tigecycline treated patients. As a result, a postmarketing requirement for thorough QT study was included as part of a labeling supplement approval letter, dated July 16, 2010.

The thorough QT study of tigecycline was initiated on January 24, 2011 and completed on May 16, 2011. The results of the study were submitted to the NDA on October 26, 2011. The results of the study were evaluated by the FDA Interdisciplinary Review Team for QT Studies. No significant QTc prolongation effect of tigecycline was detected. As a result, the Clinical Pharmacology section of Tygacil label is proposed to be amended with the following language:

No significant effect of a single intravenous dose of TYGACIL 50 mg or 200 mg on QTc interval was detected in a randomized, placebo- and active-controlled four-arm crossover thorough QTc study of 46 healthy subjects.

5.6 Pharmacokinetics, Pediatric Patients, subsection 12.3

This section was amended to include information on a single-dose safety and tolerability study in pediatric patients. The text is as follows:

A single-dose safety, tolerability, and pharmacokinetic study of tigecycline in pediatric patients aged 8-16 years who recently recovered from infections was conducted. The doses administered were 0.5, 1, or 2 mg/kg. The study showed that for children aged 12-16 years (n = 16) a dosage of 50 mg twice daily would likely result in exposures comparable to those observed in adults with the approved dosing regimen. Large variability observed in children aged 8 to 11 years of age (n = 8) required additional study to determine the appropriate dosage.

A subsequent tigecycline dose-finding study was conducted in 8-11 year old patients with cIAI, cSSSI, or CABP. The doses of tigecycline studied were 0.75 mg/kg (n = 17), 1 mg/kg (n = 21), and 1.25 mg/kg (n=20). This study showed that for children aged 8-11 years, a 1.2 mg/kg dose would likely result in exposures comparable to those observed in adults resulting with the approved dosing regimen [see *Dosage and Administration* (2.3)].

6 Review of Supporting Documents for Safety Labeling Decisions

The Sponsor submitted a separate document explaining safety labeling decisions for tigecycline titled "Justification for a safety labeling decision for tigecycline - Hypoglycemia (b) (4) Pneumonia, USPI ADR Frequency Modifications." In this document the Sponsor indicates that the Tigecycline Core Data sheet (CDS) will be

revised to include the terms Hypoglycemia (b) (4) and Pneumonia with a frequency estimate of *Common* ($\geq 1\%$ and $< 10\%$).

The inclusion of hypoglycemia is supported by the review of integrated data from Phase 3 and Phase 4 tigecycline trials. This review was prompted by individual case safety reports of hypoglycemia coincident with the administration of tigecycline. In addition to the analysis of clinical trials, the Sponsor searched the pharmacovigilance database to identify all tigecycline AE reports received cumulatively through 31 August 2010 containing Preferred Terms relevant to hypoglycemia.

The analysis of tigecycline clinical trials yielded higher incidence rates of hypoglycemia in the tigecycline versus comparator population, 2.8% vs. 1.9%, $p=0.01$, Table 3. Noteworthy, in the diabetic foot infection trial the incidence of hypoglycemia in mITT population was 15/476 (3.2%) and 5/466 (1.1%), $p=0.04$ in the tigecycline and comparator (ertapenem) arm, respectively.

Table 3: Incidence of Selected Common Adverse Events in Tigecycline Trials			
Event	Tigecycline	Comparator	Overall P-value
Hypoglycemia ¹	44/2514 (1.8%)	33/2307 (1.4%)	0.421
Hypoglycemia ²	106/3788 (2.8%)	69/3646 (1.9%)	0.011
Healing abnormal ¹	72/2514 (2.9%)	45/2307 (2.0%)	0.049
Healing abnormal ²	99/3788 (2.6%)	73/3646 (2.0%)	0.089
Pneumonia ¹	55/2514 (2.2%)	38/2307 (1.6%)	0.208
Pneumonia ²	70/3788 (1.8%)	49/3646 (1.3%)	0.096
Overall P-value: Refers to No. of Subjects data. Fisher's Exact Test P-value (2-Tail).			
¹ Studies included: 300, 301, 305, 306, 307, 308, 309, 311, and 313			
² Studies included: 300, 301, 305, 306, 307, 308, 311, 313, 315, 316, 319, 400, and 900			

The search of the pharmacovigilance database identified a total of 30 reports of hypoglycemia. Twenty-four (24) of the 30 reports originated from spontaneous notifications; five originated from sponsor-supported clinical trials ($n=5$), and one from a compassionate-use program ($n=1$). The indication for tigecycline was provided in 21 reports as follows: complicated skin and skin structure infections ($n=5$), complicated intra-abdominal infection ($n=4$), pneumonia ($n=4$), osteomyelitis ($n=4$), diabetic foot infection ($n=1$), intervertebral discitis ($n=1$), bursitis infective ($n=1$), and "head injury" ($n=1$). Medical history was provided in 22 reports; of these, 14 describing patients with a history of diabetes mellitus.

The time to event onset following tigecycline initiation was provided in 21 reports and ranged from zero days (same day as tigecycline initiation) to 18 days (median time to onset: 5 days). Event outcomes were provided in 20 reports as follows: recovered ($n=17$) or recovering ($n=3$). In 14 of these 20 reports, the event resolved or improved following tigecycline withdrawal, in three reports the event resolved while tigecycline continued, and in three reports the action taken with tigecycline was unspecified.

The Sponsor provided four representative individual case safety reports. Three out of four cases were considered life-threatening by the investigators.

1. This 73-year-old female with a history of diabetes mellitus, on tigecycline for osteomyelitis, developed profound hypoglycemia with blood glucose level less than 20 mg/dL on day 12 of therapy. Patient's concomitant medications included 22 units of insulin daily (apparently for diabetes mellitus), ramipril, bupropion hydrochloride, alprazolam, prednisone 5 mg daily, alprazolam, simvastatin, metoclopramide, and esomeprazole. Hypoglycemia resolved after administration of intravenous glucose.
2. This 82-year-old female with no history of diabetes mellitus and on no medications known to cause hypoglycemia, on tigecycline for cellulitis, developed and experienced prolonged hypoglycemia, low temperature, hyperinsulinemia and hypokalemia on day 6 of therapy. Patient's blood glucose level was found to be 19 mg/dL, serum potassium level 2.5 and serum insulin level 1861. The patient's potassium level was noted to be normal the day prior. Tigecycline was discontinued that same day and the events resolved within 36 hours with treatment. Blood insulin level was normal three days after stopping tigecycline. Blood glucose levels were monitored for the next 5 to 6 days and no low blood glucose levels were observed. Insulin C-peptide levels were normal; however, the report does not provide the date when the test was done. Concomitant therapy included clindamycin, amiodarone, Armour Thyroid, aspirin, paroxetine hydrochloride, and furosemide.
3. This 85-year-old female with no history of diabetes mellitus, on tigecycline for diverticulitis, developed hypoglycemia on day 3 of treatment with a decrease of blood glucose to 26 mg/dL. Blood glucose level the day prior was 62 mg/dL. Tigecycline was stopped, patient was apparently given glucose and blood glucose level rose to 301 mg/dL. The next day, however, blood glucose level dropped again to 26 mg/dL and eventually normalized on the 3rd day after discontinuation of tigecycline. Concomitant therapy included metoclopramide, hydrocodone bitartrate/paracetamol, ondansetron hydrochloride, metronidazole, naproxen, psyllium, zolpidem, omeprazole, aspirin, clopidogrel, ezetimibe, and sertraline.
4. This 70-year-old male with a history of diabetes mellitus, who was on tigecycline therapy for *Mycobacterium abscessus* infection of the genitor-urinary tract, experienced intermittent episodes of hypoglycemia starting from the 3rd week of treatment. Tigecycline was eventually discontinued after 11 weeks of therapy after blood glucose level was found to be 20 mg/dL. The patient recovered. Concomitant medications included insulin, clarithromycin, amikacin, an unspecified antihypertensive and antidiabetic agents.

MO comments: Considering the severity of hypoglycemia in the reported cases, the adverse event of hypoglycemia was suggested to be added to section 6.2 Post-Marketing Experience of tigecycline label. The reasons for association between tigecycline and hypoglycemia are uncertain. In some cases it may be explained by progression of the infection and sepsis. On the other hand, tigecycline is known to cause

pancreatitis, so one might speculate that tigecycline exerts some effects on the pancreas resulting in hypoglycemia. Plus, there have been reports of hypoglycemia after doxycycline use^{1,2}. The reader is referred to Attachment 1 to see the text of the respective labeling sections.

¹ Basaria S, Braga M, Moore WT. Doxycycline-induced hypoglycemia in a nondiabetic young man. *South Med J*. Nov 2002;95(11):1353-1354.

² Odeh M, Oliven A. Doxycycline-induced hypoglycemia. *J Clin Pharmacol*. Oct 2000;40(10):1173-1174.

7 Review of Diabetic Foot Infection tigecycline trial

Study Summary

Tigecycline failed to demonstrate non-inferiority in a randomized, double blind trial which compared the safety and efficacy of tigecycline versus ertapenem for the treatment of diabetic foot infections. The trial evaluated the efficacy of tigecycline in subjects with diabetic foot infections without osteomyelitis (primary study), and with osteomyelitis (osteomyelitis substudy). Of note, the tigecycline regimen in this study, 150 mg once daily, was different from that evaluated in prior phase 3 studies, which employed an initial dose of 100 mg, followed by 50 mg every 12 hours.

Subjects were randomly assigned (in a 1 to 1 ratio) to receive either tigecycline or ertapenem for up to 28 consecutive days in the primary study and (in a 2 to 1 ratio) to receive either tigecycline or ertapenem for up to 42 consecutive days in the osteomyelitis substudy.

The primary efficacy endpoint in the primary study and in the osteomyelitis substudy was the clinical response in the two co-primary populations: the clinically evaluable (CE) and the clinical modified intent-to-treat (c-mITT) populations at the test-of-cure (TOC) assessment. The noninferiority margin was -10% for the difference in the cure rates between the 2 treatments. The TOC assessment was conducted at 12 to 92 days after the last day of IV test article administration. For subjects in the osteomyelitis substudy arm, TOC assessment was conducted from 25 to 27 weeks after the last day of IV test article administration.

Efficacy

Primary study

In the analysis of clinical responses for the CE population and c-mITT populations in the primary study, tigecycline did not meet the statistical criteria for noninferiority in comparison with ertapenem at the TOC assessment (the primary endpoint). In addition, the cure rate for the tigecycline group in the c-mITT population was significantly lower than for the ertapenem group.

In the CE population, 316 of 408 subjects in the tigecycline group (77.5%) and 334 of 405 subjects in the ertapenem group (82.5%) were cured. The adjusted difference was -5.5%, with a 95% CI of -11.0% to 0.1%. For the c-mITT population of the primary study 340 of 476 subjects in the tigecycline group (71.4%) and 363 of 466 subjects in the ertapenem group (77.9%) were cured. The adjusted difference was -6.7%, with a 95% CI of -12.3% to -1.1%. Thus, tigecycline did not meet the noninferiority criteria in the two co-primary populations. In addition, in the c-mITT population, tigecycline was statistically inferior to ertapenem.

Analyses of clinical response in the modified intent-to-treat (mITT), microbiologic modified intent-to-treat (m-mITT), and microbiologically evaluable (ME) populations were consistent with the results in the co-primary efficacy populations.

Regardless of whether the infection was monomicrobial or polymicrobial, the results were consistent with those of the overall study. Eradication rates were lower and persistence rates were higher for the tigecycline group than for the ertapenem group.

Despite minimum inhibitory concentration (MIC) values that would indicate that tigecycline should have been effective, cure rates for some of the organisms were lower than expected, in particular for *Staphylococcus aureus*. In the primary study, superinfection occurred more frequently in the tigecycline group than in the ertapenem group in both the ME population (6.6% of tigecycline-treated subjects vs. 3.8% of ertapenem-treated subjects) and m-mITT population (7.1% of tigecycline-treated subjects vs. 4.0% of ertapenem-treated subjects).

Osteomyelitis Substudy

The primary efficacy endpoint in the osteomyelitis substudy was the clinical response for the CE population (cure or failure) and c-mITT population (cure, failure, or indeterminate) at the TOC assessment.

A lower percentage of subjects were cured in the tigecycline group compared with the ertapenem group in the analysis of clinical response for the CE and c-mITT populations. In the CE group a total of 12 of 38 subjects in the tigecycline group (31.6%) and 13 of 24 subjects in the ertapenem group (54.2%) were cured. In the c-mITT group 19 of 53 subjects in the tigecycline group (35.8%) and 21 of 33 subjects in the ertapenem group (63.6%) were cured. A total of 7 tigecycline-treated subjects and no ertapenem-treated subjects had an indeterminate response at the TOC assessment.

Secondary Analyses

Secondary Analyses of Clinical Response

Secondary analyses of clinical response at the TOC assessment included assessments of subjects in the microbiologically evaluable (ME) and microbiologic modified intent-to-treat (m-mITT) populations by baseline isolate and of subjects with a monomicrobial or polymicrobial infection.

In the primary study in the ME population cure rates were higher in the ertapenem group than in the tigecycline group for infections related to *Klebsiella pneumoniae*, *P. aeruginosa*, and methicillin-susceptible *Staphylococcus aureus* (MSSA). Cure rates were generally similar in the 2 treatment groups for infections due to the other isolates.

In the primary study in the m-mITT population cure rates were higher in the ertapenem group than in the tigecycline group for infections related to MSSA (Table 1). Cure rates were generally similar in the 2 treatment groups for infections due to the other isolates.

Table 1: Summary of Clinical Response at the Test-of-Cure Assessment by Baseline Isolate for Selected Pathogens in the Primary Study, m-mITT Population

Pathogen	Tigecycline		Ertapenem	
	n/N	% (95% CI)	n/N	% (95% CI)
<i>Acinetobacter calcoaceticus/baumannii</i> complex	12/15	80.0 (51.9, 95.7)	18/22	81.8 (59.7, 94.8)
<i>Enterobacter cloacae</i>	20/24	83.3 (62.6, 95.3)	30/36	83.3 (67.2, 93.6)
<i>Enterococcus faecalis</i> (Non-VRE)	58/72	80.6 (69.5, 88.9)	60/77	77.9 (67.0, 86.6)
<i>Escherichia coli</i>	23/30	76.7 (57.7, 90.1)	30/40	75.0 (58.8, 87.3)
<i>Klebsiella oxytoca</i>	13/ 18	72.2 (46.5, 90.3)	17/ 22	77.3 (54.6, 92.2)
<i>Klebsiella pneumoniae</i>	13/18	72.2 (46.5, 90.3)	19/24	79.2 (57.8, 92.9)
<i>Proteus mirabilis</i>	22/30	73.3 (54.1, 87.7)	26/33	78.8 (61.1, 91.0)
<i>Pseudomonas aeruginosa</i>	13/24	54.2 (32.8, 74.4)	15/25	60.0 (38.7, 78.9)
<i>Staphylococcus aureus</i> (non-MRSA)	100/138	72.5 (64.2, 79.7)	130/153	85.0 (78.3, 90.2)
<i>Staphylococcus aureus</i> (MRSA)	30/ 49	61.2 (46.2, 74.8)	19/ 31	61.3 (42.2, 78.2)
<i>Streptococcus agalactiae</i>	39/51	76.5 (62.5, 87.2)	43/53	81.1 (68.0, 90.6)
CI - confidence interval; m-mITT - microbiologic modified intent-to-treat; MRSA - methicillin resistant <i>Staphylococcus aureus</i> ; VRE - vancomycin-resistant <i>Enterococcus</i> .				

In the primary study and the osteomyelitis substudy, regardless of whether the infection was considered monomicrobial or polymicrobial, for both the ME and m-mITT

populations, the results are consistent with the overall study results, with higher cure rates seen in the ertapenem group compared with the tigecycline group.

Review of Safety

Deaths

A total of 10 subjects (0.8%) died during the study: 7 (1.3%) subjects in the tigecycline and 3 (0.6%) subjects in the ertapenem group. The approximately 1% difference between the treatment groups in the incidence of death is similar to that observed in prior tigecycline studies.

Most deaths in tigecycline group were related to cardiovascular system. Three patients died of myocardial infarction and one from acute cardiac failure; the other causes of death in the tigecycline group included sudden death (2) and shock suggestive of pulmonary embolism (1). In all cases the death occurred after tigecycline was stopped. Thus, 4 out of 7 patients died within 14 days after stopping the study drug and 3 patients died beyond 14 days after stopping tigecycline. In the ertapenem group one patient died of cerebrovascular accident, one patient from aspiration, and the other patient died suddenly at home.

For 2 out of 7 tigecycline deaths treatment response was reported as cure, for 5 out of 7 as undetermined.

MO comment: of note, non-fatal myocardial infarction occurred in five patients treated with tigecycline and in one patient treated with ertapenem. The reason for a higher rate of cardiac related events in the tigecycline group is not clear. One explanation is that considering a high prevalence of coronary artery disease and higher risks for myocardial infarction in diabetics, cardiac events may be expected to be a leading cause of death in this study population. Another possibility is that a decreased effectiveness of tigecycline in the treatment of DFI may result in additional stress on cardio-vascular system in this population.

Nonfatal Serious Adverse Events

During the primary study, a similar percentage of subjects experienced serious adverse events (SAEs) in each treatment group: 57 (11.9%) subjects in the tigecycline group and 50 (10.7%) subjects in the ertapenem group.

A significantly greater percentage of subjects in the primary study in the tigecycline group than in the ertapenem group developed osteomyelitis, which was the most frequently reported individual SAE in the tigecycline group (12 subjects, 2.5% vs. 3 subjects, 0.6%, respectively, $p=0.034$). The nervous system related SAEs occurred significantly less frequently in the tigecycline group than in the ertapenem group (0 subjects vs. 7 subjects, 1.5%; $p=0.007$).

In the osteomyelitis substudy, a similar percentage of subjects experienced SAEs in each treatment group: 22 (28.9%) subjects in the tigecycline group and 12 (29.3%) subjects in the ertapenem group. There were no significant differences between the groups in the incidence of any SAE, although osteomyelitis occurred in 5 subjects in the tigecycline group and in 2 subjects in the ertapenem group.

Dropouts and/or Discontinuations

During the primary study, a greater percentage of subjects discontinued investigational product because of an AE in the tigecycline group (42 subjects, 8.8%) than in the ertapenem group (27 subjects, 5.8%; $p=0.081$). In the primary study the most frequent AEs leading to discontinuation of tigecycline were nausea and vomiting (13 and 11 subjects, 2.7% and 2.3%, $p=0.007$ and $p<0.001$, respectively). In the ertapenem group nausea and vomiting led to discontinuation of the drug in 2 subjects.

Similarly, in the substudy, a greater percentage of subjects discontinued investigational product because of an AE in the tigecycline group (11 subjects, 14.5%) than in the ertapenem group (1 subject, 2.4%; $p=0.054$). The most frequent AE leading to discontinuation of tigecycline were nausea and vomiting (6 subjects in the tigecycline and 0 subjects in the ertapenem group).

In the primary study, a significantly greater percentage of subjects in the tigecycline group than in the ertapenem group (10 subjects, 2.1% vs. 2 subjects, 0.4%; $p=0.038$) withdrew from the study because of an AE. The only AEs leading to withdrawal from the study that occurred in more than 1 subject in either treatment group were infection and vomiting in the tigecycline group (2 subjects each). No single AE resulted in withdrawal from study in more than 1 subject in the ertapenem group.

Significant Adverse Events

An SAE of liver damage occurred in 1 subject in the tigecycline group in the primary study. The subject discontinued study treatment because of the event with subsequent improvement of liver functions.

MO comment: the case narrative was reviewed.

The patient was a 61-year-old female with type 2 diabetes mellitus and diabetic foot infection without osteomyelitis. Liver function abnormalities were discovered on day 13 of treatment when total bilirubin rose to 3.4 mg/dL, direct bilirubin to 2.4 mg/dL, and AST/ALT to 139/52. Tigecycline was discontinued on day 19 of treatment due to liver damage (See table).

	AST (U/L) ULN: 32	ALT (U/L) ULN: 31	Bili Total (mg/dL) ULN: 1.1	Bili Dir (mg/dL) ULN: 0.3	Alk Phos (U/L) ULN: 104	Albumin (g/dL) LLN: 3.4	INR ULN: 1.37
Baseline	25	11	1	0.3	104	2	1.8*

Day 6	34	12	0.4	0.2	97	2.1	NR
Day 13	139	52	3.4	2.4	101	1.9	NR
Day 19 – last day of treatment	147	84	6.7	6.1	133	1.9	NR
Day 40	53	21	4.1	2.4	182	2.6	1.66
Day 49	52	21	2.5	1.4	171	NR	NR

* Patient was on heparin; NR – not reported; ULN – upper limit of normal

Concomitant medications included furosemide, ranitidine, loperamide, metamizol (NSAIDs), glibenclamide (glyburide), enalapril, ketoprofen, thiethylperazine, ketorolac, and vitamin K. Ultrasound of the liver and computed tomography (CT) were performed on day 19 and revealed the fibrotic liver, moderate ascites, and portal hypertension. At the last follow up on day 49 total bilirubin was 2.5 mg/dL, direct bilirubin 1.4 mg/dL, AST/ALT 52/21 U/L, and prothrombin activity was within normal ranges.

The investigator reported that chronic hepatic damage was not related to the study treatment. The medical monitor commented that although the subject met the screening criteria for potential Hy's law cases, the case was not considered to be a Hy's law case due to preexisting liver disease and concomitant medications associated with liver abnormalities.

The medical officer agrees with the overall assessment but would like to comment that the available information does not allow one to completely rule out a Hy's law case.

In addition, hepatitis was reported in 1 subject in each of the 2 treatment groups in the osteomyelitis substudy; no cases of hepatitis occurred in the primary study. Cholestatic jaundice was reported in 1 subject, who was in the tigecycline group.

Pancreatitis was not reported during the study in either treatment group. TEAEs of increased amylase were reported infrequently and were seen in similar percentages of subjects in the tigecycline (10/477 subjects, 2.1%) and ertapenem (12/467 subjects, 2.6%) groups in the primary study. TEAEs of increased lipase were also reported in similar percentages of subjects in the 2 treatment groups in the primary study in the tigecycline (10/477 subjects, 2.1%) and ertapenem (10/467 subjects, 2.1%) groups.

Common Adverse Events

In the primary study, 605 (64.1%) subjects reported 1 or more treatment emergent adverse events (TEAEs), with significantly more subjects treated with tigecycline (339, 71.1%) than ertapenem (266, 57.0%) reporting 1 or more TEAEs ($p < 0.001$). In the osteomyelitis substudy, 93 (79.5%) subjects reported 1 or more TEAEs, with more subjects treated with tigecycline (67, 88.2%) than ertapenem (26, 63.4%) reporting 1 or more TEAEs ($p = 0.003$).

In the primary study and in the substudy, the most frequently reported TEAEs in both treatment groups were nausea, vomiting, and diarrhea. The individual TEAEs that were

reported significantly more frequently in the tigecycline group than in the ertapenem group were nausea (190 subjects, 39.8% vs. 39 subjects, 8.4%; $p<0.001$), vomiting (118 subjects, 24.7% vs. 22 subjects, 4.7%; $p<0.001$), and insomnia (15 subjects, 3.1% vs. 4 subjects, 0.9%; $p=0.018$).

In the osteomyelitis substudy, significantly more tigecycline-treated subjects reported at least 1 TEAE ($p=0.003$). The individual TEAEs that were reported significantly more frequently in the tigecycline group than in the ertapenem group were nausea (37 subjects, 48.7% vs. 7 subjects, 17.1 %; $p<0.001$), vomiting (33 subjects, 43.4% vs. 3 subjects, 7.3%; $p<0.001$), and insomnia (15 subjects, 3.1% vs. 4 subjects, 0.9%; $p=0.018$).

Hypoglycemia was reported more often in tigecycline-treated patients. In the mITT population of the primary study, when defined as glucose level ≤ 2.7 mmol/L (49.09 mg/dl), hypoglycemia was found in 15 of 476 (3.2%) tigecycline-treated patients and in 5 of 466 (1.1%) ertapenem treated patients, $p=0.04$. In the osteomyelitis substudy hypoglycemia was reported for 16 subjects (21.1%) in the tigecycline group vs. 0 subjects in the ertapenem group, $p=0.001$. One subject withdrew from the study due to hypoglycemia.

Clinical Laboratory Evaluations

In the primary study, potentially clinically important (PCI) laboratory test results occurred significantly more frequently in the ertapenem group (87.4% of subjects) than in the tigecycline group (82.6% of subjects, $p=0.045$).

Hypoglycemia, defined as glucose level ≤ 2.7 mmol/L (49.09 mg/dl) was reported significantly more often in tigecycline-treated subjects than in ertapenem treated patients in the primary study – 15 of 476 patients (3.2%) and 5 of 466 patients (1.1%) respectively, $p=0.04$; mITT population.

The analysis of liver function abnormalities have been done in subjects with normal and abnormal baseline liver functions in the primary study and osteomyelitis substudy. In the primary study in subjects with baseline normal liver functions, elevation of total bilirubin and alkaline phosphatase (ALP) above 3 times upper limit of normal was observed significantly more frequently in the tigecycline group ($p<0.001$). No increase in incidence of transaminases elevation between the tigecycline and ertapenem groups was noticed in this group.

In patients with baseline abnormal liver functions there was no difference between two groups in ALP and total bilirubin levels in response to treatment. Patients in the ertapenem group had a significant increase in AST and ALT levels, ($p=0.025$ and $p=0.048$ respectively). No difference in liver function tests was observed in subjects in the osteomyelitis substudy.

MO comments: Hypoglycemia was observed at a higher frequency in the tigecycline arm. As discussed below in the review of the Changes Being Effected Labeling Supplement from 2/11/2011, a higher rate of hypoglycemia in tigecycline as compared to comparators treated patients was also found in the review of integrated data from Phase 3 and Phase 4 tigecycline trials. Thus, we suggest adding hypoglycemia to section 6.2 Post-Marketing Experience of tigecycline label.

QTc Interval Assessment

The median change from baseline at 3 hours after administration in the nonparametric log linear QTc analysis in the tigecycline group was 5.8 ms in the primary study. This change from baseline is greater than that observed with tigecycline in most previous studies, where the median for both the tigecycline and the comparator groups was <5 ms.

There was a statistically significant QTc prolongation in the tigecycline group observed within 12 and 24 hours after dosing. For instance, within 12 hours after dosing more tigecycline than comparator subjects had increases of QT corrected (QTc) interval using the log-linear model (QTcL) ($p=0.002$), QTc using Bazett's formula (QTcB) ($p=0.001$), and QTc using Fridericia's formula (QTcF) ($p=0.012$).

MO conclusions on the DFR trial

Tigecycline failed to demonstrate noninferiority in comparison with ertapenem in patients with diabetic foot infection in the primary study and osteomyelitis substudy in both co-primary efficacy populations. In addition, in the c-mITT population in the primary study, tigecycline was statistically inferior to ertapenem. It is unclear whether a different tigecycline regimen chosen for this study, 150 mg once daily, affected the study results (the regimen tested in prior phase 3 studies consisted of an initial dose of 100 mg, followed by 50 mg every 12 hours).

The approximately 1% increase in overall mortality in tigecycline treated patients was similar to that observed in the prior phase 3 studies. The majority of deaths were related to cardiac events. Considering a high prevalence of coronary artery disease and higher risks for myocardial infarction in diabetics, cardiac events may be expected to be a leading cause of death in this study population. It is also possible, however, that a decreased effectiveness of tigecycline in the treatment of DFI may result in additional stress on cardio-vascular system in this population.

The analysis of safety data of the diabetic foot infection trial revealed a statistically significant QTc prolongation in the tigecycline when compared with ertapenem group. A thorough QT study was conducted by the sponsor and its results submitted to FDA in October 2011 have been reviewed by an Interdisciplinary Review Team for QT. Preliminary analysis, however, has not demonstrated significant QT abnormalities.

A higher rate of hypoglycemia in tigecycline as compared to comparators treated patients was observed in the DFI trial. As discussed below in the review of the CBE

Supplement similar finding were demonstrated in the review of integrated data from Phase 3 and Phase 4 tigecycline trials. Thus, we suggest adding hypoglycemia to section 6.2 Post-Marketing Experience of tigecycline label (see below).

30 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page



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/s/

DMITRI IARIKOV
07/23/2013

Rationale to include study (b) (4) As noted in the following table, data from trial (b) (4) was included in the meta-analysis limited to the approved indications.

Indication	Study Number	Tygacil	Comparator
cSSI	300	292	281
	305	274	269
	900	268	263
cIAI	301	413	412
	306	404	413
	400	236	231
	315	232	235
	(b) (4)		
CABP	308	208	210
	313	216	212
Total		2640	2628

Rationale to include Hypoglycemia in Section 6.2

The Division believes that the adverse event of symptomatic hypoglycemia should be included in section 6.2 Post-marketing experience. The Division believes that inclusion of hypoglycemia only in section 6.1 Clinical Trial Experience will not provide adequate information about this serious adverse event associated with TYGACIL use.

Cases of severe hypoglycemia observed in patients with and without diabetes receiving TYGACIL have been reported during post-marketing experience. In several cases, blood glucose decreased below 20 mg/dL and the event of hypoglycemia was viewed as life-threatening and required prolonged hospitalization. Importantly, in some cases hypoglycemia resolved after discontinuation of TYGACIL.

We also note that the Tigecycline Core Data sheet was revised to include the terms Hypoglycemia in the Adverse Reactions section.

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/s/

CARMEN L DEBELLAS
05/14/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-821/S026/S031

OTHER REVIEW(S)



DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

MEMORANDUM

DATE: August 5, 2013

FROM: Dmitri Iarikov MD PhD
Medical Officer
Division of Anti-Infective Products
Office of Antimicrobial Products
Office of New Drugs
Center for Drug Evaluation and Research

THROUGH: Sumathi Nambiar MD MPH, Acting Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Office of New Drugs
Center for Drug Evaluation and Research

SUBJECT: Approval of TYGACIL (tigecycline) 50 Milligrams/Vial ("mg/vial") Labeling Supplement and Public Citizen's Citizen Petition (FDA-2011-P-0785) Requesting That FDA Immediately Add a Black Box Warning to the Labeling, Distribute an FDA-Approved Patient Medication Guide, and Require Pfizer to Distribute a Dear Doctor Letter for TYGACIL (tigecycline) 50 mg/vial

TO: NDA 021821

I. Background

Public Citizen, a national nonprofit consumer advocacy organization, submitted a citizen petition (Petition) (docket no. FDA-2011-P-0785) on October 28, 2011, requesting that the Food and Drug Administration (FDA or 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 this adverse effect warning and the need for restricted use of TYGACIL.

The Division has reviewed the issues raised in the Petition, although FDA has not yet issued a final response. The Division and Pfizer, the Sponsor of the TYGACIL NDA (021821), have recently finalized revised labeling that will include information about increased mortality associated with the use of TYGACIL, and we have decided to approve the labeling supplements (26 and 31). The Agency will also issue a Drug Safety Communication regarding the labeling revisions related to the increased risk of mortality at the time the labeling supplements are approved. Several of the labeling revisions are related to the issues raised by the Petition.

II. Select TYGACIL Labeling Revisions

Once finalized, the TYGACIL labeling will include a boxed warning that reads as follows:

WARNING:

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. (b) (4)

Warnings and Precautions (5.1, 5.2) and Adverse Reactions (6.1)].

The WARNINGS AND PRECAUTIONS section of the TYGACIL labeling will be revised to state (new text is underlined):

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. (b) (4)

(b) (4) *Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*.

The following paragraph will be added to the ADVERSE REACTIONS section 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 (b) (4), 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 0.5% (95% CI 0.0, 1.2).

Further, the INDICATIONS AND USAGE section will be revised to state (new text is underlined):

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 (b) (4)

To reduce the development of drug-resistant 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 (b) (4) 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.

(b) (5)

(b) (5)

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/s/

DMITRI IARIKOV
08/06/2013

SUMATHI NAMBIAR
08/07/2013

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

Pre-Decisional Agency Information

Date: November 23, 2010

To: Carmen DeBellas, Pharm.D., RPh., Project Manager, DSPTP

From: Christine Corser, Pharm.D., DDMAC
Sam Skariah, Pharm.D., DDMAC

Subject: Review of Labeling for NDA 21821, S-26.
Tygacil (tigecycline) for Injection for intravenous use

As requested in your consult dated February 24, 2010, DDMAC has reviewed the draft labeling for Tygacil (S-26). DDMAC's comments are based on the substantially complete, marked-up version of the labeling received via email on November 3, 2010.

DDMAC's comments are provided in the attached, marked-up copy of the labeling.

If you have any questions about DDMAC's comments, please contact me at 6-2653 or at Christine.Corser@fda.hhs.gov.

31 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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/s/

CHRISTINE G CORSER
11/23/2010

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-821/S026/S031

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

From: DeBellas, Carmen
Sent: Friday, April 12, 2013 7:20 AM
To: 'Kirzecky, Nadia'
Subject: RE: NDA 21-821 Tygacil Label for Discussion on March 18.

Hi Nadia,

Hope this answers the question.

Hypoglycemia is included in section 6.1 among the less common adverse reactions (<1%). During our review of the clinical trial of diabetic foot infections, we noted a greater frequency of hypoglycemia reported as an adverse reaction among tigecycline-treated patients than comparator. In addition, there have been over 30 post-marketing reports of hypoglycemia, including patients with severe hypoglycemia (blood glucose <20 mg/dL).

We believe adding hypoglycemia to section 6.2 is warranted, to provide greater emphasis on adverse reaction.

Carmen

From: Kirzecky, Nadia [mailto:Nadia.Kirzecky@pfizer.com]
Sent: Tuesday, April 09, 2013 11:18 AM
To: DeBellas, Carmen
Subject: RE: NDA 21-821 Tygacil Label for Discussion on March 18.

Hi Carmen

A quick question for clarification

In the draft label you sent on 14 March, it is not clear to us why hypoglycemia is added to section 6.2 since it is already included in 6.1.

Thanks

Nadia

From: Kirzecky, Nadia
Sent: Monday, March 18, 2013 1:46 PM
To: DeBellas, Carmen
Cc: Kirzecky, Nadia
Subject: RE: NDA 21-821 Tygacil Label for Discussion on March 18.

Hi Carmen,

I have sent the questions we would like to cover with the Agency at this afternoon's call in a separate e-mail.

In addition I have a couple of clarification questions in regards to the draft label, which I think can be addressed via e-mail

1. Based on the content of the Full Prescribing Information in the draft label received on 14 March, the Dosage and Administration section is updated to include a subheading for pediatric patients. However, this change is not listed in Highlights under the heading Recent Major Changes. In addition, the draft labeling under Recent Major Changes indicates 'All-Cause Mortality', which we take to mean the addition of Warnings and Precautions, All-Cause Mortality (5.1). Can you please confirm the changes the Agency proposes to be listed under Recent Major Changes?

2. In the FPI Contents, the subheading Pediatric Patients precedes Patients with Hepatic Impairment. Could you please confirm that the order should follow what is presented in the FPI?

Many thanks,

Nadia

From: DeBellas, Carmen [mailto:Carmen.DeBellas@fda.hhs.gov]
Sent: Thursday, March 14, 2013 10:17 AM
To: Kirzecky, Nadia
Subject: NDA 21-821 Tygacil Label for Discussion on March 18.

Hi Nadia, Please find clean version of our proposed changes to your label. The track changes version was just too busy to be able to read. I have on thing I can't quite fix. The Box in the highlight section is missing the last part of the sentence and no matter how many times I try to add "Adverse Reactions (6.1)]." the margins won't allow it.

We don't expect to do a line by line review of the label but to answer any big questions you may have. We can negotiate the small stuff by email or short teleconferences later.

Hope this plan is acceptable.

Carmen

Carmen DeBellas, Pham, Rah

Regulatory Project Manager

Division of Anti-Infective Products

Office of Antimicrobial Products

Center for Drug Evaluation and Research

Phone: 301-796-1203

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/s/

CARMEN L DEBELLAS

04/12/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 21-821/S-031

CBE-0 SUPPLEMENT

Wyeth Pharmaceuticals, Inc.
Attention: Nia Tatsis, PhD
Director, Worldwide Regulatory Affairs
PO Box 8299
Philadelphia, PA 19101-8299

Dear Dr. Tatsis:

We have received your February 11, 2011, Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER:	21-821
SUPPLEMENT NUMBER:	S-031
PRODUCT NAME:	Tygacil (tigecycline)
DATE OF SUBMISSION:	February 11, 2011
DATE OF RECEIPT:	February 11, 2011

This supplemental application, submitted as a “Changes Being Effected” supplement, proposes to provide for changes to the **ADVERSE REACTIONS** section of the labeling, specifically, the adverse events of pneumonia and severe skin reaction, including Stevens - Johnson syndrome.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 12, 2011, in accordance with 21 CFR 314.101(a).

If the application is filed, the goal date will be August 11, 2011.

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3).

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size.

Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have questions, call me at (301) 796-1203.

Sincerely,

{See appended electronic signature page}

Carmen DeBellas, PharmD, RPh
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CARMEN L DEBELLAS
02/17/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR DDMAC LABELING REVIEW CONSULTATION **Please send immediately following the Filing/Planning meeting**				
TO: CDER-DDMAC-RPM			FROM: (Name/Title, Office/Division/Phone number of requestor) Division of Anti-Infective and Ophthalmology Products Carmen DeBellas, Project Manager				
REQUEST DATE 2.24.10	IND NO.	NDA/BLA NO. 21-821/S -26	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW) Labeling supplemental application				
NAME OF DRUG Tygacil	PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG 1S	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) 4/30/10				
NAME OF FIRM: Pfizer (Wyeth)			PDUFA Date: None				
TYPE OF LABEL TO REVIEW							
<table border="0"> <tr> <td> TYPE OF LABELING: (Check all that apply) X PACKAGE INSERT (PI) ☐ PATIENT PACKAGE INSERT (PPI) ☐ CARTON/CONTAINER LABELING ☐ MEDICATION GUIDE ☐ INSTRUCTIONS FOR USE(IFU) </td> <td> TYPE OF APPLICATION/SUBMISSION ☐ ORIGINAL NDA/BLA ☐ IND ☐ EFFICACY SUPPLEMENT ☐ SAFETY SUPPLEMENT X LABELING SUPPLEMENT ☐ PLR CONVERSION </td> <td> REASON FOR LABELING CONSULT ☐ INITIAL PROPOSED LABELING X LABELING REVISION </td> </tr> </table>					TYPE OF LABELING: (Check all that apply) X PACKAGE INSERT (PI) ☐ PATIENT PACKAGE INSERT (PPI) ☐ CARTON/CONTAINER LABELING ☐ MEDICATION GUIDE ☐ INSTRUCTIONS FOR USE(IFU)	TYPE OF APPLICATION/SUBMISSION ☐ ORIGINAL NDA/BLA ☐ IND ☐ EFFICACY SUPPLEMENT ☐ SAFETY SUPPLEMENT X LABELING SUPPLEMENT ☐ PLR CONVERSION	REASON FOR LABELING CONSULT ☐ INITIAL PROPOSED LABELING X LABELING REVISION
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EDR link to submission: The submission is number 138 submitted 9/30/2009							
Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.							
COMMENTS/SPECIAL INSTRUCTIONS: Mid-Cycle Meeting: [Insert Date] Labeling Meetings: [Insert Dates] Wrap-Up Meeting: [Insert Date]							
SIGNATURE OF REQUESTER Carmen DeBellas							
SIGNATURE OF RECEIVER			METHOD OF DELIVERY (Check one) X eMAIL ☐ HAND				

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21821	SUPPL-26	WYETH PHARMACEUTICA LS INC	TYGACIL

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/s/

CARMEN L DEBELLAS
02/24/2010