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APPLICATION NUMBER:

211158Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	505(b)(2)
Application Number(s)	NDA 211158
Priority or Standard	Standard
Submit Date(s)	10/2/2017
PDUFA Goal Date	8/2/2018
Division/Office	Division of Anti-Infective Products / Office of Antimicrobial Products
Reviewer Name(s)	Rama Kapoor, M.D.
Review Completion Date	6/25/18
Established Name	Tigecycline
(Proposed) Trade Name	Tigecycline
Applicant	Amneal Pharmaceuticals
Formulation(s)	Tigecycline for Injection USP, 50 mg/vial
Dosing Regimen	Multiple
Indication(s)/Population(s)	Complicated skin and skin structure infections; Complicated intra-abdominal infections; Community-acquired bacterial pneumonia;
Recommendation on Regulatory Action	From the clinical reviewer perspective, this 505 (b)(2) application for tigecycline for the indications of complicated skin and skin structure infections, complicated intraabdominal infections, and community-acquired bacterial pneumonia may be approved.

1. Executive Summary

The proposed drug product, Tigecycline for Injection, 50 mg/vial is a new formulation of tigecycline for injection submitted by Amneal Pharmaceuticals (Amneal).

The Listed drug product which forms the basis for this application via the 505(b)(2) New Drug Application (NDA) pathway is Tygacil ® (tigecycline) for Injection, 50 mg/vial, approved in 2005 via NDA 21821. The drug product proposed by Amneal Pharmaceuticals (Amneal), Tigecycline for Injection, 50 mg/vial, is a new formulation of tigecycline which differs from the listed drug in the excipients used in the formulation with respect to the (b) (4) applicant's product contains L--arginine whereas the listed drug contains lactose monohydrate. Otherwise, the applicant's product has the same active and inactive ingredients, strength, route of administration, and conditions of use as the listed drug, tygacil for injection. Each tigecycline vial contains 50 mg of tigecycline lyophilized powder for reconstitution and intravenous

infusion.

TYGACIL (tigecycline) for injection, NDA 021821, was originally approved for use in the U.S. on June 15, 2005, and is indicated in patients 18 years or older for the treatment of complicated skin and skin structure infections, intra-abdominal infections, and community-acquired bacterial pneumonia. This application was ineligible to use the Abbreviated New Drug Application (ANDA) pathway because the formulation contains a qualitative difference in inactive ingredients.

No clinical data have been submitted in this NDA as the Applicant is relying on the Agency's previous findings of efficacy and safety for Tygacil for approval of the proposed drug product. The majority of the information submitted in the NDA relates to the chemistry, manufacturing, and controls used in the manufacture of the proposed tigecycline drug product.

The Applicant has included an in vivo bioavailability/bioequivalence waiver request with this submission due to similarities between the proposed and the listed drug.
However, because of the difference in the excipients, there is potential that the disposition kinetics of tigecycline in the proposed drug product may not match with the listed drug product; therefore, the Applicant has used an alternative approach to measure bioavailability or establish bioequivalence.

2. Benefit-Risk Assessment

This 505(b)(2) NDA application for tigecycline relies on FDA's previous findings of safety and effectiveness for the listed drug, Tygacil[1]. The benefit-risk assessment for this product, tigecycline remains unchanged as for the listed product, Tygacil (tigecycline). Tigecycline has been approved by the FDA and widely marketed since June 2005. The tigecycline has undergone numerous clinical trials where safety has been assessed formally, prior to and following approval. No new clinical studies were submitted in this NDA. Tigecycline remains a viable treatment option for approved indications in situations when alternative treatments are not suitable for reasons related to allergies, microbial resistance, renal impairment or other circumstances that may preclude the use of other antibacterial drugs.

As mentioned above, the proposed formulation of tigecycline differs from the reference formulation in that L-arginine has been substituted for lactose (b) (4). The administration of Amneal's product would result in an initial daily arginine exposure of 150 mg (Day 1 of therapy) and a daily exposure of 100mg over the remaining duration of treatment.

[1] TYGACIL® (tigecycline) for injection, USPI, 2016.

These are comparable or lower than the concentration of arginine in other FDA approved products. There is no evidence suggesting that proposed amounts of L-arginine included in the product would impact safety or efficacy of the tigecycline formulation in any significant way.

3. Regulatory Background

A Pre-Investigational New Drug Application (PIND 128826) file for tigecycline for injection was Opened on April 25, 2016. Amneal submitted a Type B Pre-IND (PIND 128826) meeting request on April 25, 2016, to discuss the development plans and appropriate regulatory pathway for their proposed Tigecycline for Injection USP, 50 mg/vial formulation.

NDA 211158 for tigecycline Injection 50 mg/mL was submitted pursuant to section 505(b)(2) on October 2, 2017. There had been no other significant presubmission regulatory activity related to this NDA.

4. Product Information

Tigecycline is a tetracycline-class antibacterial drug. Tigecycline inhibits protein translation in bacteria by binding to the 30S ribosomal subunit, blocking entry of aminoacyl tRNA into the A site of the ribosome and preventing incorporation of amino acid residues into elongating peptide chains. Tigecycline is considered bacteriostatic; however, tigecycline demonstrated bactericidal activity against *Streptococcus pneumoniae* and *Legionella* pneumophila. The antibacterial spectrum of tigecycline includes gram-positive and gram-negative organisms (including aerobic and anaerobic species), including methicillin-resistant *Staphylococcus aureus* (MRSA), *Legionella pneumophila*, and some Mycobacteria. Tigecycline is not active against *Pseudomonas aeruginosa* and has decreased activity against Proteus, Providencia, and *Morganella species*.

4.1. Arginine

Arginine is the excipient used in the proposed tigecycline formulation. Arginine is an aminoacid, synthesized endogenously from citrulline, primarily by mammalian epithethial cells of the small intestine and the proximal tubule of the kidney and in most instances, in sufficient quantities for the healthy adult human. However, in cases of disease such as inflammation, infection or dysfunction of the kidneys or small intestine (the major site of biosynthesis of arginine), insufficient amounts of arginine may be produced to meet all the metabolic demands, since

arginine is involved in many important roles of normal metabolism. The average intake of arginine from the diet of a healthy adult is estimated at between 2.5 and 5 g/day of which about 60% is metabolized by the gastrointestinal tract prior to systemic distribution. The normal plasma concentrations of free L-arginine in a healthy individual has been reported as between 41 and 114 µmol/L or 15.1 ± 2.6 µg/ mL, which is higher than the amounts that would be administered with the proposed tigecycline formulation.

5. Important Safety Issues with Consideration to Related Drugs

Potential risks associated with tetracycline class of antibacterial drugs include anti-anabolic events as represented by blood urea nitrogen (BUN) increased and azotemia, central nervous system side effects including light-headedness, vertigo or dizziness, hypersensitivity, photosensitivity, pseudotumor cerebri, acute pancreatitis, and fungal infections, in particular, vulvovaginal fungal infections. Pill esophagitis is also noted particularly with doxycycline.

The one potential cause for concern is the observation that in comparative clinical trials, tigecycline was found to be associated with an increase in all-cause mortality as compared to comparators. The numerical excess deaths seen in patients treated with tigecycline has led the FDA to issue an FDA Drug Safety Communication (Drug Safety Announcement - 1 September 2010; http://www.fda.gov/Drugs/DrugSafety/ucm224370.htm). The FDA communication indicated that death occurred in 150 of 3,788 (4.0%) patients treated with tigecycline and 110 of 3,646 (3.0%) patients treated with another antibacterial, with the adjusted risk for all-cause mortality being 0.6% (95% CI = 0.1 to 1.2). There was no significant difference from the comparator treated groups in all-cause mortality (mITT population, 4,242 patients, FEM, OR = 1.47, 95% CI = 0.96 to 2.27, P=0.08); however, there was numerically higher mortality in the tigecycline treated groups.

In September 2013, the tigecycline label was revised to include a boxed warning containing the following information:

> **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.**

6. Significant Efficacy/Safety Issues Related to Other Review Disciplines

Reader is referred to the reviews conducted by respective disciplines.

7. Sources of Clinical Data and Review Strategy

No clinical studies have been conducted by the applicant and only data from published sources have been provided.

8. Review of Efficacy

No new information changing prior assessments of the risk-benefit profile of tigecycline have been identified.

9. Review of Safety

No new information changing prior assessments of the risk-benefit profile of tigecycline have been identified.

10. Safety reports identified through Postmarket Experience

The Applicant has submitted literature references of few isolated case reports of 'drug reactions' attributed to tigecycline, which included angiokeratoma, hyperpigmentation of the skin, leukemoid reaction, and hypofibrinogenemia. These isolated case reports are briefly summarized below.

Case Report # 1: Angiokeratoma: A 59 year old patient, who had been on chronic immunosuppressive therapy for severe rheumatoid arthritis, and who had completed a 6- week course of intravenous tigecycline for an unrelated soft tissue infection. Several days following cessation of therapy with tigecycline, the patient developed two dark colored papules, one on each of her lower extremities. Biopsy revealed that the lesions were angiokeratomas. Seven weeks following the initial appearance of papule, six of the angiokeratomas had spontaneously resolved. Due to the proximity of the initial lesions to the use of tigecycline, and the long (>60 hours) half-life of the drug, and the disappearance of the lesions following continued discontinuation of the tigecycline, it was hypothesized that the tigecycline was likely

responsible.[2]

Case Report # 2. Brown-gray hyperpigmentation of the skin: A 65 year old patient was treated with tigecycline for 102 days for a sacral decubitus ulcer with osteomyelitis. After about two and a half months into treatment, brown-gray hyperpigmentation of the skin on the trunk and upper arms was observed, that was similar to the hyperpigmentation seen following minocycline use. Because tigecycline is a derivative of minocycline, it was supposed to be the culprit drug and was discontinued. However, the subject died two weeks later before the lesion had a chance to resolve.[3]

Case Report #3. Leukemoid reaction: A 62 year old man with aspiration pneumonia who had failed prior multiple antibacterial drug treatments, was treated with tigecycline and vancomycin for pneumonia as well as voriconazole for a concomitant fungal infection. With the improvement of pneumonia, the vancomycin and voriconazole were stopped, and the patient remained on tigecycline. After three weeks of therapy with tigecycline, he developed a fever and a leukemoid reaction with a WBC of 38 x 10^9/L. There was no evidence of progression of the infection, so the tigecycline was discontinued, and the patient was treated with steroids. The fever and leukemoid reaction resolved in 3 days, suggesting this may have been a sensitivity reaction to the tigecycline.[4]

Case Report #4. Hypofibrinogenemia: A 74 year old female patient with end stage renal disease, was treated with tigecycline for an infection with multi-drug resistant Acinetobacter baumannii infection following a hip replacement surgery, who developed increased international normalized ratio (INR), prolonged aPTT, and severe hypofibrinogenemia, followed by elevation of transaminases, cholestasis, and anemia. Ultrasonography and computed tomography revealed no underlying pathological entities. Tigecycline was discontinued, and the patient underwent daily hemodialysis and received multiple fresh frozen plasma transfusions. No alternative cause was identified. Her clinical and laboratory status improved after few days.[5]

[2] Michael Isaacs, Jami Miller, MD; A report of tigecycline-associated angiokeratoma formation:J AM ACAD DERMATOL; MAY 2016
[3] S. J. Vandecasteele et al; Tigecycline Induced Hyperpigmentation of the Skin: Open Forum Infectious Diseases; 9 February 2016.
[4] Shao et al; Tigecycline-induced Drug Fever and Leukemoid Reaction- A Case Report; Medicine Volume 94, Number 45, November 2015
[5] Nikolas Sabanis et al: Hypofi brinogenemia induced by tigecycline: a potentially life-threatening coagulation disorder; Infectious Diseases, 2015; 47: 743–746

11. Labeling Recommendations

The Applicant has not submitted the proposed labeling in Pregnancy and Lactation Labeling Rule (PLLR) format initially. Updated labeling in PLLR format was re-structured to be consistent with the PLLR, as follows:

Pregnancy, Section 8.1
The "Pregnancy" subsection of labeling was formatted in the PLLR format to include: "Risk Summary," and "Data" subheadings.

Lactation, Section 8.2
The "Lactation" subsection of labeling was formatted in the PLLR format to include the "Risk Summary" and "Clinical Considerations" subheading.

Patient Counseling Information, Section 17
The "Patient Counseling Information" section of labeling was updated to correspond with changes made to sections 8.1 and 8.2 of labeling.

The labeling is currently undergoing revision based on recommendations from different disciplines.

12. Risk Evaluation and Mitigation Strategies (REMS)

Not Applicable

13. Postmarketing Requirements and Commitments

Not Applicable

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/s/

RAMA KAPOOR
06/25/2018