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APPLICATION NUMBER:

21158Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader and Division Director Review

Date	(electronic stamp)
From	Balajee Shanmugam Ph.D., Sumathi Nambiar MD MPH
Subject	Cross-Discipline Team Leader and Division Director Review
NDA #	211158
Applicant Name	Amneal Pharmaceuticals
Date of Submission	October 10, 2017
PDUFA Goal Date	August 8, 2018
Proprietary Name/Established (USAN) Name	Tigecycline for injection* (tigecycline)
Dosage Forms / Strength	Injection 50 mg/vial
Proposed Indications	<ul style="list-style-type: none"> • Complicated and Uncomplicated Skin and Skin Structure Infections • Complicated Intra-abdominal Infections • Community-Acquired Pneumonia
Action:	Approval

**No proprietary/trade name was proposed for the drug product*

1.0 Introduction

This 505(b)(2) NDA submitted by Amneal Pharmaceuticals provides for a new injectable formulation of Tigecycline to be used for the treatment of the same indications as listed in the table above and in the drug labeling for the listed drug (LD), Tygacil® (tigecycline for injection). The drug product proposed in this NDA, tigecycline for injection, 50 mg/vial is a sterile lyophilized powder but the presented formulation differs from the listed drug in that it contains different (b) (4). In view of the similarities between the proposed drug product and the LD, a biowaiver for conducting in-vivo bioequivalence studies was requested by the Applicant. The Applicant is relying on the Agency's previous findings of effectiveness and safety for Tygacil® for approval of the proposed drug product.

2.0 Background

Tigecycline is a tetracycline class compound which exerts antibacterial action by inhibiting 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. Tygacil® (tigecycline for injection) 50 mg/vial, originally approved in 2005 is indicated for the treatment of complicated and uncomplicated skin and skin structure infections, complicated intra-abdominal infections, and community-acquired bacterial pneumonia.

3.0 Product Quality

The Product Quality ATL for this application was covered initially by Dorota Matecka, Ph.D. and later by Balajee Shanmugam, Ph.D. The OPQ review team is listed in the IQA dated June 9, 2018.

The Chemistry, Manufacturing and Controls (CMC) information for tigecycline drug substance in support of this NDA is referenced to DMF (b) (4) held by the manufacturer, (b) (4). The DMF, previously reviewed for another submission was found adequate as documented in the review dated April 18, 2018 and also supports this NDA. Additional CMC information (such as elemental analysis) provided in the NDA was found acceptable by the drug substance reviewer.

The proposed drug product Tigecycline for Injection, 50 mg/vial, is a sterile, lyophilized orange (b) (4) cake or powder supplied in a 5 mL Type I glass vial with a (b) (4) stopper and (b) (4) flip off seal. L-Arginine (b) (4) and sodium hydroxide and/or hydrochloric acid (pH adjusters) are the excipients used in the proposed formulation. A 6% overfill is used in the vial to allow withdrawal of the labeled amount of tigecycline. The product should be reconstituted and diluted prior to administration. The Applicant tightened the limit for the impurity, (b) (4) to NMT (b) (4)% to conform to the USP monograph for tigecycline for injection. Adequate in-use stability data to support the diluents listed in the proposed package insert and co-administration with drugs listed in the package insert is provided. The (b) (4) impurity mentioned above did increase to (b) (4)% at 24 h in the constituted product but there was no pharmacology/toxicology concern since this trend is also observed in other approved tigecycline products. The drug product specification included tests typical of the dosage form and found acceptable. The stability data of 24-months long-term and 6-months accelerated for three registration batches supports an expiration dating of 24-months when stored at 25°C (b) (4). CMC information submitted in support of the quality of the drug product was found acceptable by the drug product reviewer.

The product quality microbiology review (covering all sterility information) and biopharmaceutics review (assessing the data to support bridging to the listed drug) found the information submitted to the NDA acceptable.

The drug substance is manufactured by (b) (4) and the drug product is manufactured at the Gland Pharma Limited facility in India. An overall recommendation of “Approve” has been issued by the Office of Process and Facilities.

Based on the assessment of the information submitted, the OPQ review team recommended approval of the NDA from Product Quality Perspective.

4.0 Pharmacology/Toxicology

This 505(b)(2) NDA relies on FDA's previous findings of safety and efficacy for the LD. Since the nonclinical toxicity of tigecycline has been characterized in both *in vitro* and *in vivo* studies during development of Tygacil, the Applicant did not submit any new non-clinical studies to support this NDA.

The proposed formulation contains an excipient, L-arginine at a concentration of 50 mg per vial. Since this excipient has been used in previously approved product at higher concentrations for the same route of administration and because about 60% of the average dietary intake (estimated at between 2.5 and 5 g/day) is metabolized by the gastrointestinal tract prior to reaching the systemic system, the levels used in the proposed formulation is deemed safe. This is also supported by the published trial in fasted healthy volunteers.

Based on the evaluation of the information presented, Dr. Alapatt recommends approval of the NDA from a pharmacology/toxicology perspective.

5.0 Biopharmaceutics

Biopharmaceutics review assess the waiver request for the conduct of bioavailability /bioequivalence studies. Based on supporting data, such comparison of the drug product to the LD for osmolality and pH, an *in vitro* protein binding study, the differences in the inactive ingredients are not expected to affect the disposition kinetics of tigecycline in the proposed drug product when administered via the intravenous (IV) route and the disposition kinetics should be similar after IV administration of these two products. Based on the evaluation of the submitted information, the biopharmaceutics reviewer concluded that the proposed drug product has been adequately bridged to the LD and therefore, per 21 CFR 320.24 (b)(6), an *in vivo* pharmacokinetic study is not needed.

6.0 Clinical Microbiology

No new clinical microbiology information was submitted in this application. Dr. Sheikh, Ph.D. notes that in a previous communication to the applicant, it was recommended that the Microbiology section of the package insert be updated in accordance to the 21st Century Cures Act. The Applicant complied and subsequently submitted an amended label. The reviewer finds the NDA acceptable from a clinical microbiology perspective.

7.0 Clinical Pharmacology

The one new clinical study report which consists of literature review and analysis of existing pharmacokinetic data was assessed by the Office of Clinical Pharmacology. The clinical pharmacology reviewer notes that the proposed formulation is reasonable since higher amounts

of arginine have been used in previously approved parenteral products and therefore this NDA is acceptable from clinical pharmacology perspective.

8.0 Clinical Efficacy/Safety

The resubmission did not provide new clinical data and the Applicant is relying on FDA's previous findings of safety and efficacy for Tygacil. Dr. Kapoor, MD, clinical reviewer for this application notes that no new information changing prior assessments of the risk-benefit profile of tigecycline have been identified. Since the Applicant did not submit the proposed labeling in Pregnancy and Lactation Labeling Rule (PLLR) format initially, an update to the labeling in PLLR format was restructured to be consistent with the PLLR and these included:

- Pregnancy, Section 8.1 - to include "Risk Summary" and "Data" subheadings
- Lactation, Section 8.2 - to include "Risk Summary" and "Clinical Considerations" subheadings

Patient Counseling Information, Section 17 - Updated to correspond with changes made to sections 8.1 and 8.2 of labeling.

Dr. Kapoor recommends approval of the NDA.

9.0 Labeling

Labeling issues have been adequately resolved based on reviews from several offices including, Office of Prescription Drug Products (OPDP) (reviewed by David Foss, PharmD), and the Division of Medication Error Prevention and Analysis (DMEPA) (reviewed by Deborah Myers, RPh, MBA) and Division of Pediatric and Maternal Health (DPMH).

10.0 Other Regulatory Issues

The NDA submitted by Amneal Pharmaceuticals is based on the LD Tygacil (tigecycline) for injection, 50mg/vial (NDA #021821). The active ingredient, tigecycline, in the proposed drug product is the same as in the LD, however, the formulation of the proposed product is qualitatively different in that arginine is used (b) (4).

This application was not presented to the Anti-Microbial Drugs Advisory Committee (AMDAC) as there were no issues that needed input from the AMDAC.

11.0 Regulatory Action

We agree with the recommendations made by the review team that this NDA covered under 505(b)(2) be approved, relying on the Agency's prior findings of safety and effectiveness of the listed drug product Tygacil (NDA 021821).

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SUMATHI NAMBIAR
08/01/2018