CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211158Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	211158
Submission Date	9/30/17
Drug	Tigecycline
OCP Reviewer	Cristina Miglis, Pharm.D, MSc, BCPS
OCP Team Leader	Zhixia (Grace) Yan, Ph.D.
OCP Division	DCP4
OND Division	DAIP
Sponsor	Amneal Pharmaceuticals Inc.
Submission Type	505(b)(2)
Formulation	IV Injection, 50 mg/vial
Indication	For the treatment as an antibacterial indicated in patients 18 years of age and older for: • Complicated skin and skin structure infections • Complicated intra-abdominal infections • Community-acquired bacterial pneumonia
Dosage and Administration	• Initial dose of 100 mg, followed by 50 mg every 12 hours administered intravenously over approximately 30 to 60 minutes. • Severe hepatic impairment (Child Pugh C): Initial dose of 100 mg followed by 25 mg every 12 hours.

Background

Amneal Pharmaceuticals Inc. has developed Tigecycline for Injection, 50 mg/vial with the intent of obtaining FDA approval via the 505(b)(2) New Drug Application (NDA) pathway. The Listed Drug (RLD) that forms the basis for the NDA is intravenous Tygacil® (NDA # 021821; PF Prism CV). The proposed formulation is identical to the RLD in active ingredient, strength, route of administration and dosage regimen. The qualitative difference between the Sponsor's proposed formulation and the RLD lies in (b) (4); Arginine is used in Amneal's formulation whereas Lactose Monohydrate is used in the RLD. A comparison of the proposed product and reference listed drug is presented in **Table 1**.

The Spsonsor has included one new clinical study report in their 505(b)(2) NDA application. This report aims to demonstrate the effect of the differences between excipients in reference and test Tigecycline products, on the disposition kinetics of Tigecycline in human subjects. The report includes a summary of an extensive literature search and results of a pharmacokinetic model using data from one select pharmacokinetic study, in which human Arginine plasma concentration data was digitized and modeled [1]. These data were used to fit to a two compartment IV infusion model using Pheonix Winnonlin (V6.4). The pharmacokinetic parameters obtained were then used to simulate the plasma Arginine levels of a 30-minute infusion of 50 mg L-Arginine, a dose equivalent to that in the Sponsor's proposed product (**Figure 1**). Given that

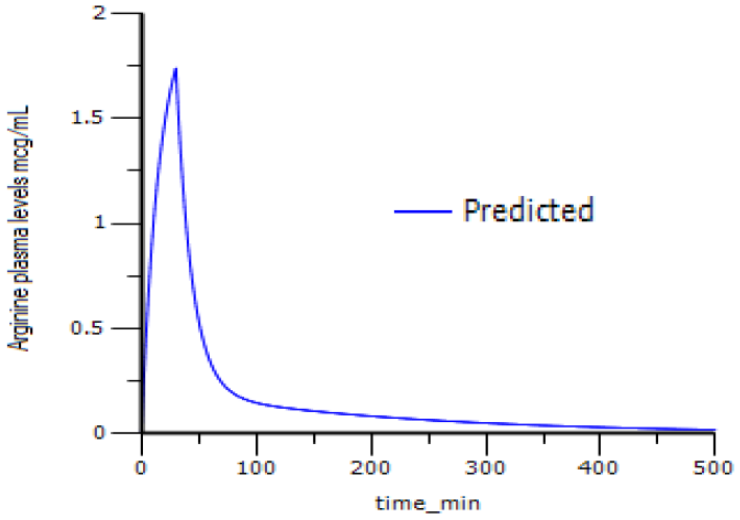
average baseline L-Ariginine levels in healthy volunteers are reportedly 15.1 +/- 2.6 ug/mL, the Sponsor claims that administration of the proposed dose of 50 mg will not produce any significant changes in normal baseline levels. Based on this literature search, the Sponsor also claims that Arginine and Tigecycline do not share any disposition mechanisms or transporters; thus, an interaction at the disposition level between Tigecycline and Arginine is not expected.

The Sponsor has also included with its NDA an *in vivo* bioavailability/bioequivalence waiver request for the proposed Tigecycline product. The Agency agreed in a written response dated July 6, 2016 that no bridging studies are necessary.

Table 1. Formulation Comparison Between the RLD (TYGACIL®) and Amneal's Proposed Product (Tigecycline for Injection).

Ingredient	**Tygacil (Tigecycline) (50 mg/vial)**	**Amneal Pharmaceuticals Tigecycline for Injection (50 mg/vial)**	**Function**
Tigecycline	50 mg	50 mg	Active Ingredient
L-arginine	None	50 mg	(b) (4)
Lactose Monohydrate	100 mg	None	
HCl/NaOH	Quantity sufficient for adjustment of pH	To pH (b) (4)	Adjustment of pH

Figure 1: Simulation of plasma levels of L-Arginine after administration of a 30-minute infusion of a dose of 50 mg in human volunteers.



Recommendation

The Office of Clinical Pharmacology, Division of Clinical Pharmacology 4 has reviewed the application. One new clinical study report was submitted, which consists of a literature review and analysis of existing pharmacokinetic data. The Sponsor has also submitted an in vivo bioavailability/bioequivalence waiver request that will be reviewed by Office of Pharmaceutical Quality, Office of New Drug Products, Divisoin of Biopharmaceutics. From a Clinical Pharmacology perspective, the proposed formulation is reasonable as higher amounts of Arginine have been used (b) (4) in previously approved parenteral products. For example, each 1 gram vial of Aztreonam contains 1.6 grams of Arginine, with Aztreonam doses as high as 2 grams every 6 hours recommended in the package insert. This equates to an Arginine total daily dose of 6.4 grams as compared to 100mg total daily Arginine in the Sponsor's proposed Tigecycline dosing regimen. No new clinical studies were submitted at this time. Thus, this application is acceptable from a clinical pharmacology perspective.

References

1. Tangphao O, et al. Pharmacokinetics of intravenous and oral L-Arginine in normal volunteers. J Clin Pharmacol. 1999. 47;261-266.

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